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<p>(54) Title: ANTI-INFLAMMATORY COMPOUNDS</p> <div style="text-align: center;"> <p>(I)</p> </div> <p>(57) Abstract</p> <p>This invention relates to anti-inflammatory compounds, methods of making such compounds and methods of using such compounds having structure (I).</p>		

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ANTI-INFLAMMATORY COMPOUNDS

Background of the Invention

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1. Field of Invention

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This invention relates to triphenylpropanamide compounds which are useful in treating inflammations but which do not demonstrate the side effects normally associated with other anti-inflammatory treatments such as glucocorticoids. This invention also relates to methods for making and using the compounds of the invention.

2. Prior Art

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Glucocorticoids are the only agents which reduce all the symptoms that are manifested in chronic adrenocortical disorder and hyperfunction, allergies, rheumatoid arthritis, lupus, inflammatory bowel disease, pneumonia, bronchial asthma, hematological disorders, dermatitis and eczema. Glucocorticoids also reduce immunological response in organ transplants. The undesired side effects of these agents include hypertension, atherosclerosis, diabetes, hyperglycemia, bone thinning and electrolyte imbalance.

25

Mechanistically, glucocorticoids bind to the glucocorticoid receptor (GR) on the surface of leukocytes and the resulting glucocorticoid -GR complex migrates into the cell nucleus. There, the complex interacts with transcription factor AP-1 (activating protein-1), inhibiting its induction of genes that produce inflammatory cytokines and collagenase, thereby repressing the inflammatory process. However, the complex also activates GRE (glucocorticoid response element), a transcriptional activator of genes which are responsible for the

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undesirable side effects mentioned heretofore. The most desirable anti-inflammatory medication would inhibit AP-1 without activating GRE.

Steroids, such as dexamethasone and prednisone have been found to exhibit potent antiinflammatory activity, but also exhibit the previously-mentioned side effects.

Heretofore, there has been no antiinflammatory agent found which does not cause side effects. Thus, new chemical agents are needed which would have the desired antiinflammatory effect without causing the side effects mentioned above.

Prior art compounds which relate to the triphenylcyclopropyl and triphenylpropyl compounds of the invention are as follows: U.S. Patent No. 3,941,833 (Gognaco) describes certain amino derivatives of 2,2-diaryl-cyclopropane. They are described as being useful for the treatment of disorders of the cardiovascular system. They are intended for systemic use. There is no indication in this patent that such compounds can or should be administered topically. Nor is there any indication that such compounds would be useful for treating inflammation of the skin.

Gilbert, et al. in *J. Med. Chem.* 1983, 26, 693-699 report triphenylpropylidene amines and nitriles as inhibitors of prostaglandin synthetase

Blank et al. in *J. Med. Chem.* 1969, 12, 873-876 describe the inhibition by 2,3,3-triphenylpropylamines of the biosynthesis of aldosterone without altering deoxycorticosterone or corticosterone levels.

Schultz et al. in *J. Med. Chem.* 1967, 10, 717-724 describe diphenylpropanamides which are hypocholesteremic in rats and inhibit penicillin excretion in dogs.

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Burch et al. in *Proc. Natl. Acad. Sci. USA* 1991, 88, 355-359 describe fluorenyl propanamides which inhibit localized inflammatory reactions in mice.

German Patent No. 2,726,993 (Gognaco) describes 1-substituted 2,2-diphenylcyclopropanes. The patent indicates that they are useful as vasodilators and blood pressure lowering agents. They are intended for systemic use. There is no indication in this patent that such compounds can or should be administered topically. Nor is there any indication that such compounds would be useful for treating inflammation of the skin.

Belgian patent No. BE 855689 (Hexachemie S. A. Fr.) describes 2,2-diphenylcyclopropylmethanamides with vasodilator activity.

Precigoux, et al. describe the compound 4,4'-(3-Acetemido-2-phenylpropylidene) diphenol diacetate in *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, C41 (8), 1985, pp. 1244-1246.

Falkenstein et al. describe certain phenylaziridine compounds in "Single electron transfer versus nucleophilic ring opening in reactions of cis-trans pairs of activated 2-phenylaziridines. Strong influence of nitrogen pyramid for N-benzoylaziridines.", *J. Org. Chem.*, 1993, 58, pp. 7377-7381.

Stamm et al. describe other aziridines in "Reactions with aziridines. 53. Arene hydrides. 9. Intermediate substitution in the formation of a benzylic anion by an aromatic radical anion as observed with 1-benzoyl-2-phenylaziridine." *Chem. Ber.*, 1990, 123, pp. 2227-2230. Stamm et al. also described related aziridine structures in "Reductive ring opening of N-benzoylaziridine by anthracene hydride (anion of 9,10-dihydroanthracene) via base-induced fragmentation of the intermediate carbonyl adduct." *J. Org. Chem.*, 1989, 54, pp. 1603-1607. However, none of these publications describe the structures of this invention nor do they indicate that such compounds would be useful in treating inflammation.

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Therefore, it is an object of this invention to provide one or more compounds capable of treating inflammatory diseases.

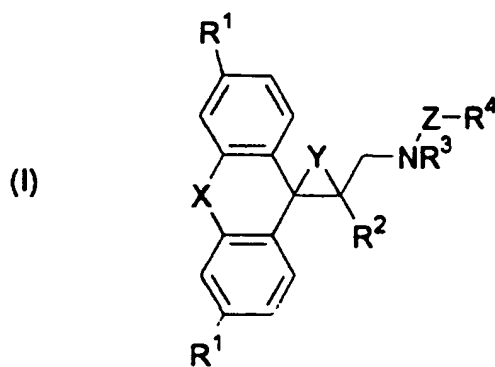
It is a further object of this invention to provide compounds capable of treating inflammatory diseases without causing side effects similar to those caused by glucocorticoids.

It is yet another object of this invention to provide a method of making compounds for treating inflammatory diseases.

Another object of this invention is to provide a method of treating inflammatory diseases in mammals by administration of the compounds of this invention.

Summary of the Invention

This invention relates to novel non-steroidal small molecule organic compounds that exhibit the beneficial therapeutic properties of glucocorticoids, that may be free of glucocorticoid-like side effects, and which may have a high affinity for the human glucocorticoid receptor (hGR). The compounds of this invention have the following structure (I):



- 5 -

wherein X, R¹, R², R³, R⁴, R⁵, W, Y and Z are as defined hereinafter.

These compounds are useful in treating inflammatory diseases in humans and other mammals. The compounds of the present invention may also be useful in the treatment of other disorders, such as chronic adrenocortical disorder and hyperfunction, allergies, rheumatoid arthritis, lupus, use as immunosuppressants in organ transplant, pneumonia, bronchial asthma, hematological disorders, dermatitis and eczema. The present invention is also directed to pharmaceutical compositions containing the compounds of formula I and methods of treating inflammation and other conditions employing such compounds.

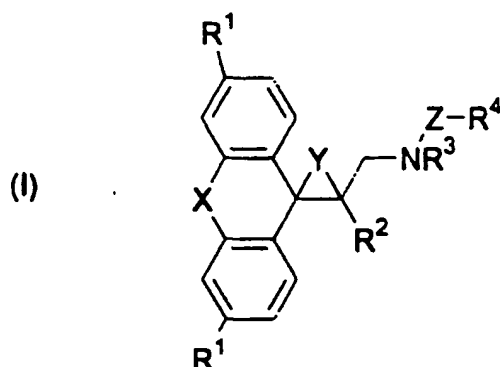
As used herein unless otherwise noted, alkyl and alkoxy, whether used along or as part of a substituent group, include straight and branched chains. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl, 2-methylpentyl, etc. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Of course, if the alkyl or alkoxy substituent is branched there must be at least three carbon atoms in the group.

The term "aryl" as used herein along or in combination with other terms indicates aromatic hydrocarbon groups such as phenyl or naphthyl. The term heteroaryl means aromatic groups, incorporating as part of the aromatic ring, 1 or 2 hetero atoms selected from any of S, O, or N. With reference to substituents, the term "independently" means that when more than one of such substituent is possible such substituents may be the same or different from each other.

Detailed Description of the Preferred Embodiments

The present invention is directed to compounds of the general formula I:

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X may be a single bond or is chosen from hydrogen, sulfur or NR^6 ; wherein R^6 is selected from the group consisting of: hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl, in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido, or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile. X may further be selected from $-(CH_2)_n$ wherein n is an integer from 1 to 3; $-HC=CH-$; and $-CH_2W$ wherein W may be oxygen, sulfur or NR^6 . Of course when X is hydrogen, it does not represent a connection between the phenyl rings;

wherein R^1 is from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halogen such as chlorine, fluorine, iodine or the like, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

wherein R^2 is a phenyl group in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halo, carboxy,

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carboalkoxy, amino, amido, sulfonamido or nitrile; or a heteroaromatic ring such as substituted- or unsubstituted thiophene, furan, pyrrole, pyridine, or the like;

wherein Y is -CH₂- or hydrogen;

5 wherein R³ is chosen from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; phenylloweralkyl in which
10 said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

 wherein Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone; and

15 wherein R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted-
20 or unsubstituted thiophene, furan, pyrrole, pyridine, or the like or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted-or unsubstituted thiophene, furan, pyrrole, pyridine or the like. When X is hydrogen, S or NR⁵, R⁴ may be phenyl wherein said phenyl group is substituted with hydrogen or with one to
25 three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile.

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Preferably, the compounds of this invention have formula (I) above wherein X is hydrogen and Y is hydrogen. Also preferable are the compounds of this invention wherein R¹ is selected from the group consisting of hydrogen and halogen. More preferably, R¹ is fluorine.

5 More preferably, the compounds of this invention have formula (I) above wherein X is hydrogen, Y is hydrogen, R¹ is selected from the group consisting of hydrogen and halogen and R² is selected from the group consisting of phenyl, halophenyl, or methylenedioxy. Most preferably, R¹ is fluorine or hydrogen and R² is 4-chlorophenyl, 4-iodophenyl or 3,4-methylenedioxyphenyl.

10 Also preferable are compounds of formula (I) wherein X is hydrogen, Y is hydrogen, R¹ is selected from the group consisting of hydrogen and halogen, R² is selected from the group consisting of phenyl, halophenyl, or alkoxyphenyl and R³ is selected from the group consisting of hydrogen and lower alkyl. Most preferably, R³ is hydrogen.

15 Another preferable group of compounds of formula (I) are those wherein X is hydrogen, Y is hydrogen, R¹ is selected from the group consisting of hydrogen and halogen, R² is selected from the group consisting of phenyl and halophenyl, R³ is selected from the group consisting of hydrogen and lower alkyl and Z is carbonyl. Preferably, R⁴ is selected from the group consisting of straight-chain alkyl, phenyllower alkyl and heteroaromatic lower alkyl. Even
20 more preferably R⁴ is a heteroaromatic lower alkyl group. Most preferably, R⁴ is 2-thiophenemethylene or 4-chlorophenylmethylene.

25 The compounds of this invention are useful in treating inflammatory diseases such as rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, dermatitis, and eczema. They may also be therapeutically beneficial in the treatment of other disorders including lupus, chronic adrenal disorder and hyperfunction, allergies, pneumonia, bronchial asthma, hematological

disorders and as immunosuppressants in organ transplant. They may be administered topically or systemically.

The compounds of this invention have been found to bind to the hGR. However, because they differ in structure from glucocorticoids, they appear to bind selectively to the hGR, without binding to DNA and activating the GRE. This results in a potentially much lower incidence of side effects, and, consequently, longer periods of administration with greater overall efficacy and relief.

The compounds of this invention are optically active. The beneficial therapeutic activity may reside with either enantiomer or they may be most active and advantageously utilized in racemic mixtures.

Examples of particularly preferred compounds include: 98, 29, 33, 72, 90, 96, 84, 80, 47, 97, 123, 127, 128, 132, 140, 141, 145, 147, 150, 153, 165, 167, 173, 174, 175, 176, 177, 178, 179, and 180. Exemplary compounds are as follows:

N-(2-thiophene)acetyl-2, 3, 3-triphenylpropylamine.

N-(5-methylthiophene)acetyl-2-phenyl-3, 3-bis (4-fluorophenyl)propylamine.

N-(3-indolyl) acetyl-2, 3, 3-triphenylpropylamine.

N-(2-carbonyl-5-methylthiophene)-2-(9H-fluoreny-9-yl)-2-phenylethylamine.

N-(2-chlorophenyl)acetyl-1, 2, 2-triphenylcyclopropylmethylamine.

N-(2-thienyl)carbonyl-1, 2, 2-triphenylcyclopropylmethylamine.

N-(phenyloxy)carbonyl-1, 2, 2-triphenylcyclopropylmethylamine.

N-(4-chlorophenyloxy)carbonyl-1, 2, 2-triphenylcyclopropylmethylamine.

N-(2-pyridine)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

N-(4-n-butoxyphenyl)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

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N-(2, 4-difluorophenyl)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

N-(2-thiophene)carbonyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

5 N-(3-cyanophenyl)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

N-(2, 4-difluorophenyl)carbonyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

10 N-(4-fluorophenyl)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

N-(4, 5-dichlorophenyl)carbonyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

N-(3-methylphenyl)acetyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.

15 N-(phenyl)acetyl-2-(4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.

N-(5-chloro-2-benzothiophene)acetyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.

N-(2, 4-difluorophenyl)carbonyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.

20 N-(4-trifluoromethylphenyl)acetyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.

N-(phenyl)acetyl-2-(4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.

N-(4-fluorophenyl)acetyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.

25 N-(3, 5-bis-tri fluorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.

N-(4- chlorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.

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N-(3, 4-dichlorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-
diphenylpropylamine.

N-(2-fluorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-
diphenylpropylamine.

5 N-(2-fluorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-
diphenylpropylamine.

N-(4-fluorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-
diphenylpropylamine.

10 N-(4-trifluoromethylphenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-
diphenylpropylamine.

N-(3, 5-bistrifluoromethylphenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-
diphenylpropylamine.

N-(2-thiophene) carbonyl-2- (4-iodomethylphenyl)-3, 3- diphenylpropylamine.

15 N-(5-methyl-2-thiophene)carbonyl-2- (4-iodomethylphenyl)-3, 3-
diphenylpropylamine.

N-(4-chlorophenyl)carbonyl-2- (3, 4-methylenedioxyphenyl)-3, 3-
diphenylpropylamine.

N-(2-propyl) carbonyl -1, 2, 2-triphenylcyclopropylmethylamine.

20 The compounds of this invention may also include the respective
hydrates of compounds specifically identified herein.

The compounds of formula I may be prepared according to the following
reaction schemes.

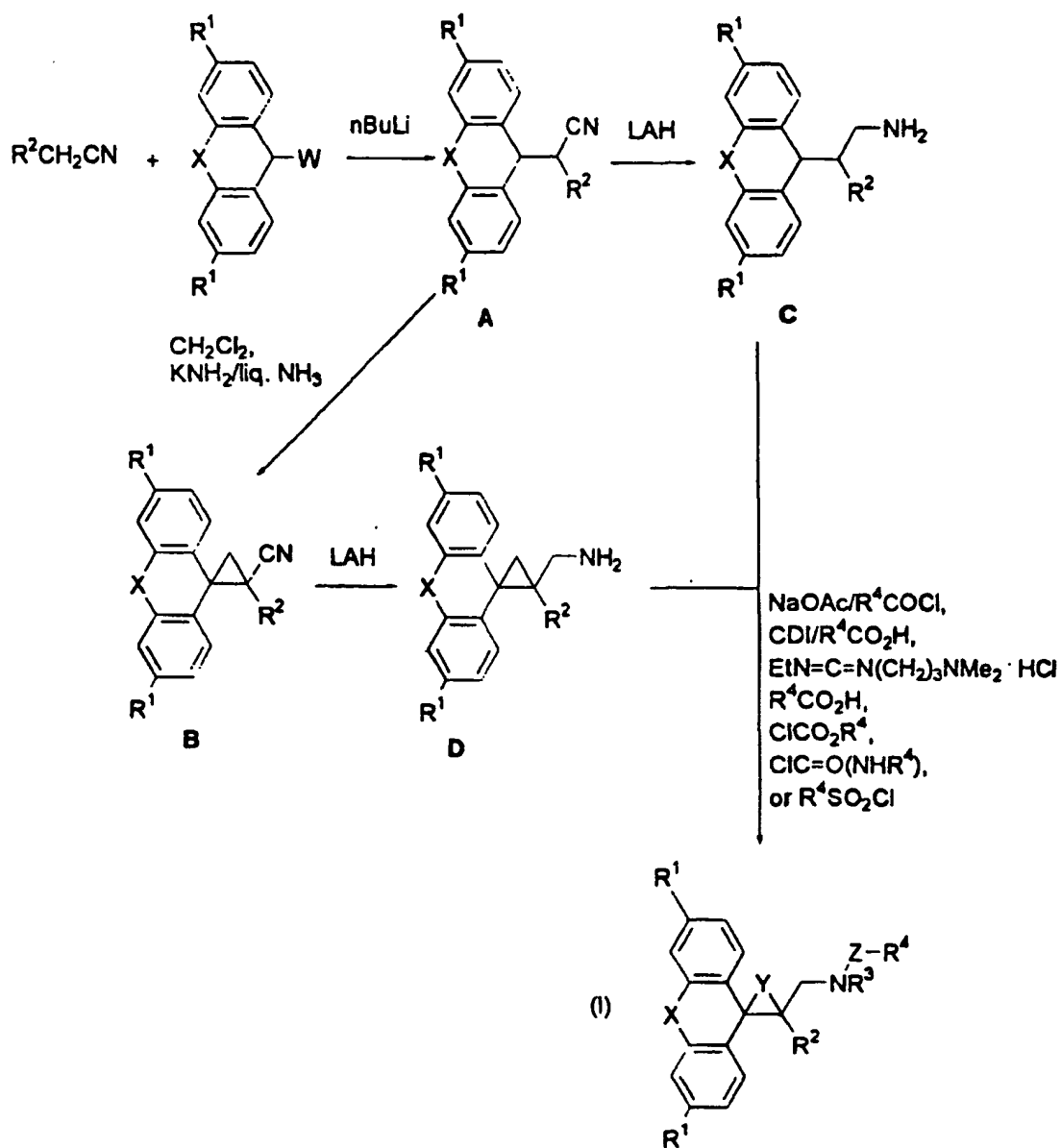
25 Reaction Scheme 1 displays a method of making the compounds of
formula I, where R^1 - R^5 , W, X, Y and Z are as defined above. Treatment of a
suitable substituted or unsubstituted diphenyl methyl-, fluorenyl-, or 10,11-
dihydro-5H-dibenzo[1,d]cyclohepten-4-yl chloride or bromide with an aryl- or
heteroaryl acetonitrile using n-BuLi and the like or phase-transfer conditions,

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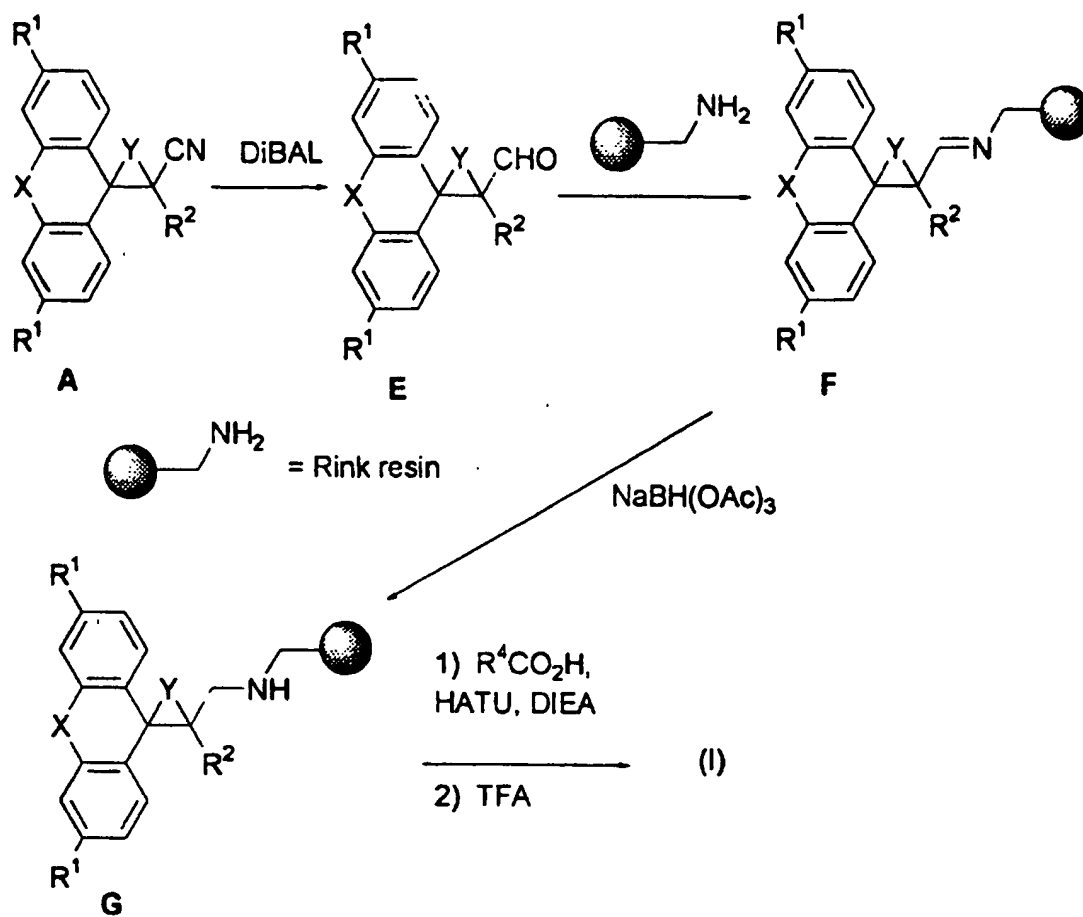
afford nitrile intermediates of structure A. Reduction of A with LAH, $\text{NaBH}_4/\text{BH}_3$ and the like leads to the formation of amines C. Treatment of structure A with methylene chloride in the presence of potassium amide/liquid ammonia leads to the formation of structure B. Reduction of the nitrile group of structure B with LAH, $\text{NaBH}_4/\text{BH}_3$ and the like leads to an amine of structure D. By reacting C or D with acid chlorides as set forth below in Scheme I in combination with bases such as NaOAc and the like, organic acids in combination with activating agents such as 1,1'-carbonyldiimidazole and the like, sulfonyl chlorides, chloroformates, isocyanates, isothiocyanates, or a suitable organic sulfonyl chloride, compounds of structure I are obtained. Optionally, nitriles of structure A, when treated with diisobutylaluminum hydride (DiBAL), are converted to aldehydes of structure E. Treatment of E with Rink resin affords resin-bound imines of structure F which are reduced with sodium triacetoxy borane to resin-bound imines of structure G. Treatment of G with an appropriate acid in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (hereinafter referred to as "HATU") and diisopropylethylamine (DIEA) affords compounds of structure I. Compounds of structure I may also be prepared by the reaction of amines of structure H with appropriate carboxylic acids in the presence of resin-bound 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide which is prepared from 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide and Merrifield resin.

Scheme 1

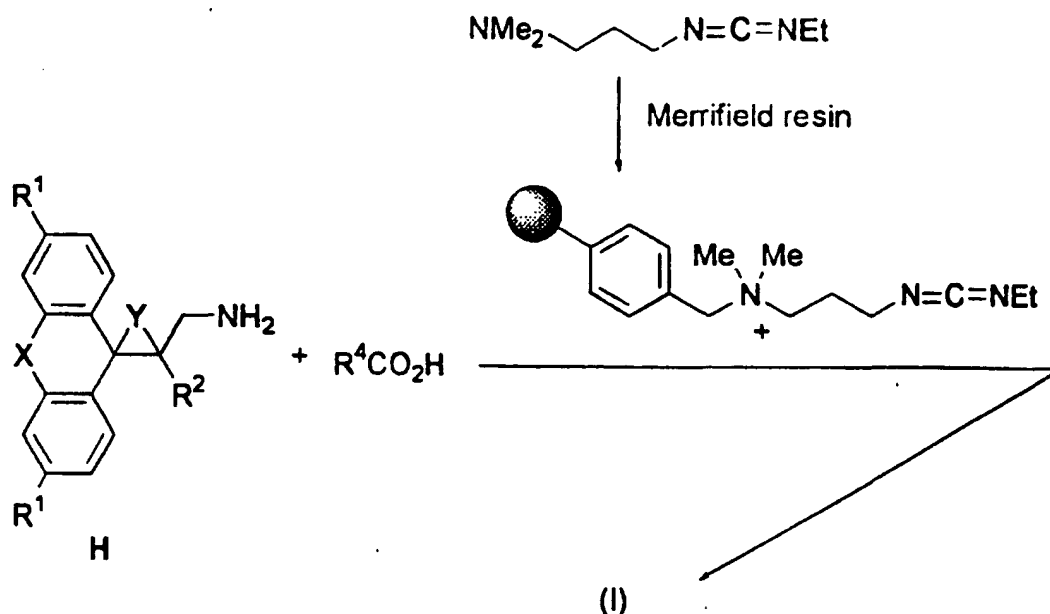
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- 15 -



To prepare the pharmaceutical compositions of this invention, one or more compounds or salts thereof of the invention, as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed.

Thus for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations, such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage form, in which case solid pharmaceutical carriers

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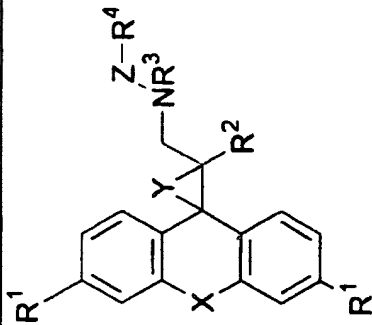
are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable
5 suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will preferably contain per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, from about 50 to about 100 mg of the active ingredient, although other unit dosages may be
10 employed. The compounds of this invention may also be applied or utilized topically. If the delivery parameters of the topically active pharmaceutical or cosmetic agent so require, the topically active composition of this invention may preferably be further composed of a pharmaceutically or cosmetically acceptable vehicle capable of functioning as a delivery system to enable the
15 penetration of the topically active agent into the skin. In alternative embodiments, the topically active pharmaceutical or cosmetic composition may be optionally combined with other ingredients such as moisturizers, foaming agents, cosmetic adjuvants, anti-oxidants, surfactants, foaming agents, conditioners, humectants, fragrances, viscosifiers, buffering agents,
20 preservatives, and the like in an amount which will not destroy the active ingredient in order to produce cosmetic or pharmaceutical products.

The topically active pharmaceutical or cosmetic composition should be applied in an amount effective to treat inflammation of mammalian skin. As used herein "amount effective" shall mean an amount sufficient to
25 ameliorate inflammation of mammalian skin. A composition containing 0.001-10.0% of active agent is applied to the skin surface when amelioration of an inflammatory condition is desired. Preferably, a composition containing 0.05-5.0% of active agent is applied to the skin surface such that, based

16a

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Table 1. Physical and Biological Properties of Triphenylpropylamine and Triphenylcyclopropyl amine Derivatives



											hPR	
											hGR	% inh
cmp	R ¹	R ²	R ³	R ⁴	X	Y	Z	mp, °C	IC ₅₀ (nM)	10 μM		
1	H	Ph	H	PhCH ₂	H, H	H, H	CO	146.0 - 147.0	890	-0.2		
2	H	Ph	H	2-ClPhCH ₂	H, H	H, H	CO	140.5-141.2	134	-23		
3	H	Ph	H	4-ClPhCH ₂	H, H	H, H	CO	168.4-170.9	480	4		
4	H	Ph	H	4-MePhCH ₂	H, H	H, H	CO	142.3-143.6	528	12		
5	H	Ph	H	2-MeOPhCH ₂	H, H	H, H	CO	156.9-158.9	62%			
6	H	Ph	H	4-MeOPhCH ₂	H, H	H, H	CO	157-159	910			
7	H	Ph	H	3,4-MeOPhCH ₂	H, H	H, H	CO	123-124.5	910	11.6		
8	H	Ph	H	2,6-diClPhCH ₂	H, H	H, H	CO	165.2-166.5	340	3		
9	H	Ph	H	3,4-diClPhCH ₂	H, H	H, H	CO	65-68	1480			
10	H	Ph	H	2-CF ₃ PhCH ₂	H, H	H, H	CO	109-111.5	780	15		
11	H	Ph	H	3-CF ₃ PhCH ₂	H, H	H, H	CO	108.8-111.3	830	20		

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12	H	Ph	H	4-CF ₃ PhCH ₂	H ₁ H	H ₁ H	CO	119.5-120.3	1500	15
13	H	Ph	H	Ph ₂ CH	H ₁ H	H ₁ H	CO	178.7-179.8	780	
14	H	4-ClPh	H	PhCH ₂	H ₁ H	H ₁ H	CO	151.5-152.7	72	18
15	4-F	Ph	H	PhCH ₂	H ₁ H	H ₁ H	CO	87.5-89.7	21	
16	4-F	Ph	H	2-ClPhCH ₂	H ₁ H	H ₁ H	CO	127.3-129.4	45	
17	4-F	Ph	Me	PhCH ₂	H ₁ H	H ₁ H	CO	86.9-88.2		
18	H	Ph	H	Ph	H ₁ H	H ₁ H	CO	161.5-163	610	14.1
19	H	Ph	H	Ph(CH ₂) ₂	H ₁ H	H ₁ H	CO	107.4-109.0	141	24
20	H	Ph	H	2-MeOPh(CH ₂) ₂	H ₁ H	H ₁ H	CO	137-140	58	9
21	H	4-ClPh	H	2-MeOPh(CH ₂) ₂	H ₁ H	H ₁ H	CO	122.2-123.5	57	21
22	H	Ph	H	2-ClPh(CH ₂) ₂	H ₁ H	H ₁ H	CO	135.0-135.8	103	
23	4-F	Ph	H	2-MeOPh(CH ₂) ₂	H ₁ H	H ₁ H	CO	78.9-80.9	22	
24	H	Ph	H	Ph(CH ₂) ₃	H ₁ H	H ₁ H	CO	78.1-81.0	670	10
25	H	Ph	H	PhCH ₂	H ₁ H	H ₁ H	SO ₂	172.9-174.2	210	
26	H	Ph	H	4-MePh	H ₁ H	H ₁ H	SO ₂	139.7-142.1	175	
27	H	Ph	H	PhSO ₂ CH ₂	H ₁ H	H ₁ H	CO	186.9-187.5	67	
28	H	Ph	H	4-MePhSO ₂ CH ₂	H ₁ H	H ₁ H	CO	190.3-191.9	57	
29	H	Ph	H	2-thiopheneCH ₂	H ₁ H	H ₁ H	CO	130-132	8	28.3
(+)			(+)				24			
(-)			(-)				>800			
30	H	Ph	H	5-Me-2-thiophene	H ₁ H	H ₁ H	CO	183.5-185	50	
31	4-F	Ph	H	2-thiopheneCH ₂	H ₁ H	H ₁ H	CO	84.9-85.3	8	
32	4-F	Ph	H	5-Me-2-thiopheneCH ₂	H ₁ H	H ₁ H	CO	127.9-128.9	7	
33	H	4-IPh	H	2-thiopheneCH ₂	H ₁ H	H ₁ H	CO	127-130	8.6	
34	H	4-ClPh	H	2-thiopheneCH ₂	H ₁ H	H ₁ H	CO	126.3-127.0	21	17
35	H	4-ClPh	H	3-thiopheneCH ₂	H ₁ H	H ₁ H	CO	126.4-127.9	54	
36	H	Ph	H	3-thiopheneCH ₂	H ₁ H	H ₁ H	CO	135-138	25	22
37	H	Ph	H	2-thiophene(CH ₂) ₃	H ₁ H	H ₁ H	CO	105.5-106.9	500	4

16c

38	H	Ph	H	2-thiopheneCH=CH(O)	H, H	H, H	CO	217.3-218.9	189
39	H	Ph	H	3-thiopheneCH=CH	H, H	H, H	CO	204.8-206.5	727
40	H	Ph	H	2-thiophene	H, H	H, H	SO ₂	169.0-170.9	151
41	H	4-ClPh	H	2-thiophene	H, H	H, H	SO ₂	180.4-181.9	491
42	H	Ph	H	3-thiophene	H, H	H, H	CO	153.5-154.7	68
43	H	Ph	H	2-benzothiophene	H, H	H, H	CO	218.3-218.8	495
44	H	Ph	Me	2-thiopheneCH ₂	H, H	H, H	CO	107-109.3	133
45	H	Ph	H	2-thiophene	H, H	H, H	CO	139-142	31
46	H	2-thio	H	2-thiopheneCH ₂	H, H	H, H	CO	138.2-139.9	723
47	H	Ph	H	3-indoleCH ₂	H, H	H, H	CO	89-93	416
48	H	Ph	H	3-indole(CH ₂) ₂	H, H	H, H	CO	100-114	605
49	H	Ph	H	2-pyridylCH ₂	H, H	H, H	CO	120.1-121.7	200
50	H	Ph	H	NHPh	H, H	H, H	CO	205-206	
51	H	Ph	H	2-MeOPhNH	H, H	H, H	CO	203-204	32%
52	H	Ph	H	2-ClPhNH	H, H	H, H	CO	210-211	273
53	H	Ph	H	2-FPhNH	H, H	H, H	CO	190-191	293
54	H	Ph	H	PhCH ₂ NH	H, H	H, H	CO	170-171	219
55	H	Ph	H	2,4-diClPhCH ₂ NH	H, H	H, H	CO	166-167	121
56	H	Ph	H	PhO	H, H	H, H	CO	128-129	310
57	H	Ph	H	4-ClPhO	H, H	H, H	CO	159-160	294
58	H	Ph	H	4-FPhO	H, H	H, H	CO	150-151	240
59	H	Ph	H	2-NaphthO	H, H	H, H	CO	151-152	155
60	H	Ph	H	Pr	H, H	H, H	CO	88-89	446
61	H	Ph	H	i-Pr	H, H	H, H	CO	114-115	584
62	H	Ph	H	n-Bu	H, H	H, H	CO	78-79	121
63	H	Ph	H	i-Bu	H, H	H, H	CO	112-113	316
64	H	Ph	H	i-Bu	H, H	H, H	CO	143-144	296
65	H	Ph	H	CH ₂ CO ₂ Et	H, H	H, H	CO	103-105.5	937
66	H	Ph	H	PhCH ₂	SB	H, H	CO	148.7-150.8	888
67	H	Ph	H	2-MeOPhCH ₂	SB	H, H	CO	159.4-161.1	23%

16d

68	H	Ph	H	2-ClPhCH ₂	SB	H, H	CO	162.4-164.2	46%
69	H	Ph	H	2-CF ₃ PhCH ₂	SB	H, H	CO	153.9-155	15%
70	H	Ph	H	2-MeOPh(CH ₂) ₂	SB	H, H	CO	173.5-175.6	53%
71	H	Ph	H	2-thiopheneCH ₂	SB	H, H	CO	128.7-130.5	820 16
72	H	Ph	H	5-Me-2-thiophene	SB	H, H	CO	158.3-160.5	33%
73	H	Ph	H	PhCH ₂	(CH ₂) ₂	H, H	CO	172.7-174.6	770
74	H	Ph	H	2-MeOPh(CH ₂) ₂	(CH ₂) ₂	H, H	CO	134.3-136.8	388
75	H	Ph	H	2-thiopheneCH ₂	(CH ₂) ₂	H, H	CO	175-177.5	363
76	H	Ph	H	3-thiopheneCH ₂	(CH ₂) ₂	H, H	CO	167.3-169.3	571
77	H	Ph	H	5-Me-2-thiophene	(CH ₂) ₂	H, H	CO	172.1-173	882
78	H	Ph	H	PhCH ₂	H, H	CH ₂	CO	150-152	1200 6
79	H	Ph	H	3,4-MeOPhCH ₂	H, H	CH ₂	CO	131-133.5	1000 24.5
80	H	Ph	H	2-ClPhCH ₂	H, H	CH ₂	CO	128.5-130.5	955 -11
81	H	Ph	H	2-MeOPh(CH ₂) ₂	H, H	CH ₂	CO	187.5-189	709
82	H	Ph	H	CHPh ₂	H, H	CH ₂	CO	166-169	510 -20.4
83	H	Ph	H	n-propyl	H, H	CH ₂	CO	149-150	573 45
84	H	Ph	H	i-propyl	H, H	CH ₂	CO	167-168	612 15.3
85	H	Ph	H	2-Me-propyl	H, H	CH ₂	CO	142-143	68% 7.2s
86	H	Ph	H	t-butyl	H, H	CH ₂	CO	121-122	665 12.6
87	H	Ph	H	n-butyl	H, H	CH ₂	CO	122-123	681 19.8
88	H	Ph	H	2-thiopheneCH ₂	H, H	CH ₂	CO	135-137	425
89	H	Ph	H	3-thiopheneCH ₂	H, H	CH ₂	CO	130-135	570 22
90	H	Ph	H	2-thiophene	H, H	CH ₂	CO	152.5-155	612
91	H	Ph	H	5-Me-2-thiophene	H, H	CH ₂	CO	168-170.5	421
92	H	Ph	H	PhNH	H, H	CH ₂	CO	209-210	1488 -1
93	H	Ph	H	2-FPhNH	H, H	CH ₂	CO	235-236	17% 33.9

Cmpd	R ¹	R ²	R ³	R ⁴	X	Y	Z	Mass	Ion	Molecular	% Inhibition
98	H	3,4-(OCH ₂ O)Ph	H	4-ClPhCH ₂	H, H	H, H	CO	484.0	486	MOCH	
94	H	H	Ph	H	2-MeOPhNH	H, H	CH ₂	CO		246-247	13%
95	H	H	Ph	H	PhCH ₂ NH	H, H	CH ₂	CO		231-232	4%
96	H	H	Ph	H	PhO	H, H	CH ₂	CO		146-147	9.9
97	H	H	Ph	H	4-ClPhO	H, H	CH ₂	CO		171-172	157
99	H	3,4-(OCH ₂ O)Ph	H	2-thiopheneCH ₂	H, H	H, H	H, H	CO	455.6	456	35
100	H	3,4-(OCH ₂ O)Ph	H	3-Me-5-Cl-benzo-	H, H	H, H	H, H	CO	554.1	554, 556	18
				thiophene-2-CH ₂							
101	H	3,4-(OCH ₂ O)Ph	H	5-Cl-benzo-	H, H	H, H	H, H	CO	540.1	540, 542	26
				thiophene-2-CH ₂							
102	H	3,4-(OCH ₂ O)Ph	H	2-pyridineCH ₂	H, H	H, H	H, H	CO	450.5	451	51
103	H	3,4-(OCH ₂ O)Ph	H	3-CF ₃ phenylCH ₂	H, H	H, H	H, H	CO	517.5	518	37
104	H	3,4-(OCH ₂ O)Ph	H	3,5-di-CF ₃ phenylCH ₂	H, H	H, H	H, H	CO	585.5	586	52
105	H	3,4-(OCH ₂ O)Ph	H	4-NO ₂ phenylCH ₂	H, H	H, H	H, H	CO	494.5	495	24
106	H	3,4-(OCH ₂ O)Ph	H	4-BuOphenylCH ₂	H, H	H, H	H, H	CO	521.7	522	52
107	H	3,4-(OCH ₂ O)Ph	H	2-MeOphenylCH ₂	H, H	H, H	H, H	CO	479.6	480	28
108	H	3,4-(OCH ₂ O)Ph	H	3,5-di-MeOphenylCH ₂	H, H	H, H	H, H	CO	509.6	510	38
109	H	3,4-(OCH ₂ O)Ph	H	phenylCH ₂	H, H	H, H	H, H	CO	449.5	450	22
110	H	3,4-(OCH ₂ O)Ph	H	3-FphenylCH ₂	H, H	H, H	H, H	CO	467.5	468	20
111	H	3,4-(OCH ₂ O)Ph	H	2,4-diF-phenylCH ₂	H, H	H, H	H, H	CO	485.5	486	60
112	H	3,4-(OCH ₂ O)Ph	H	2,4-di-Cl-phenylCH ₂	H, H	H, H	H, H	CO	518.4	518, 520	36
113	H	3,4-(OCH ₂ O)Ph	H	3,4-diCl-phenylCH ₂	H, H	H, H	H, H	CO	518.4	518, 520	31
114	H	3,4-(OCH ₂ O)Ph	H	phenylthioCH ₂	H, H	H, H	H, H	CO	481.6	482	41
115	H	3,4-(OCH ₂ O)Ph	H	3-thiophene	H, H	H, H	H, H	CO	441.5	442	28
116	H	3,4-(OCH ₂ O)Ph	H	2-thiophene	H, H	H, H	H, H	CO	441.5	442	62
117	H	3,4-(OCH ₂ O)Ph	H	phenyl	H, H	H, H	H, H	CO	435.5	436	28
118	H	3,4-(OCH ₂ O)Ph	H	2-MeO-phenyl	H, H	H, H	H, H	CO	465.5	466	38

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119	H	3,4-(OCH ₂ O)Ph	H	2-indole	H _i H	H _i H	CO	474.6	475	31
120	H	3,4-(OCH ₂ O)Ph	H	3,5-di-CF ₃ phenyl	H _i H	H _i H	CO	571.5	572	27
121	H	3,4-(OCH ₂ O)Ph	H	3-NO ₂ -phenyl	H _i H	H _i H	CO	480.5	481	10
122	H	3,4-(OCH ₂ O)Ph	H	3-NO ₂ -4-Me-phenyl	H _i H	H _i H	CO	494.5	495	33
123	H	3,4-(OCH ₂ O)Ph	H	3-CN-phenyl	H _i H	H _i H	CO	460.5	461	51
124	H	3,4-(OCH ₂ O)Ph	H	phenylethyl	H _i H	H _i H	CO	463.6	464	35
125	H	3,4-(OCH ₂ O)Ph	H	4-IBu-phenyl	H _i H	H _i H	CO	491.6	492	31
126	H	3,4-(OCH ₂ O)Ph	H	4-Me-phenyl	H _i H	H _i H	CO	449.5	450	46
127	H	3,4-(OCH ₂ O)Ph	H	2,4-diF-phenyl	H _i H	H _i H	CO	471.5	472	61
128	H	3,4-(OCH ₂ O)Ph	H	4-F-phenyl	H _i H	H _i H	CO	453.5	454	54
129	H	3,4-(OCH ₂ O)Ph	H	2-Cl-phenyl	H _i H	H _i H	CO	470.0	470, 472	41
130	H	3,4-(OCH ₂ O)Ph	H	4-Cl-phenyl	H _i H	H _i H	CO	470.0	470, 472	37
131	H	3,4-(OCH ₂ O)Ph	H	3,5-diCl-phenyl	H _i H	H _i H	CO	504.4	504, 506	18
132	H	3,4-(OCH ₂ O)Ph	H	4,5-diCl-phenyl	H _i H	H _i H	CO	504.4	504, 506	69
133	H	3,4-(OCH ₂ O)Ph	H	2-Me-phenyl	H _i H	H _i H	CO	449.5	450	46
134	H	3,4-(OCH ₂ O)Ph	H	4-biphenylCH ₂	H _i H	H _i H	CO	525.6	526	29
135	H	4-CF ₃ -Ph	H	2-thiopheneCH ₂	H _i H	H _i H	CO	479.6	480	31
136	H	4-CF ₃ -Ph	H	2-thiophene	H _i H	H _i H	CO	465.5	466	38
137	H	4-CF ₃ -Ph	H	2-Cl-phenyl	H _i H	H _i H	CO	494	494, 496	45
138	H	4-CF ₃ -Ph	H	3,4-diCl-phenylCH ₂	H _i H	H _i H	CO	542.4	542, 544	33
139	H	4-CF ₃ -Ph	H	2,4-diCl-phenyl	H _i H	H _i H	CO	528.4	528, 530	42
140	H	4-CF ₃ -Ph	H	3-Me-phenylCH ₂	H _i H	H _i H	CO	487.6	488	57
141	H	4-CF ₃ -Ph	H	phenylCH ₂	H _i H	H _i H	CO	473.5	474	66
142	H	4-CF ₃ -Ph	H	2-pyridineCH ₂	H _i H	H _i H	CO	474.5	475	39
143	H	4-CF ₃ -Ph	H	4-MeS-phenylCH ₂	H _i H	H _i H	CO	519.6	520	19
144	H	4-CF ₃ -Ph	H	2-MeO-4-Cl-phenyl	H _i H	H _i H	CO	524	524, 526	33
145	H	4-CF ₃ -Ph	H	5-Cl-benzo- thiophene-2-CH ₂	H _i H	H _i H	CO	564.1	564, 565	54
146	H	4-CF ₃ -Ph	H	2-Cl-phenylCH ₂	H _i H	H _i H	CO	508.0	508.2	39
147	H	4-CF ₃ -Ph	H	2,4-diF-phenylCH ₂	H _i H	H _i H	CO	509.5	510.2	55

16g

148	H	4-CF ₃ -Ph	H	2-MeO-phenylCH ₂	H, H	H, H	CO	503.6	504	42
149	H	4-CF ₃ -Ph	H	3,5-diMeO-phenylCH ₂	H, H	H, H	CO	533.6	534	42
150	H	4-CF ₃ -Ph	H	4-CF ₃ -phenylCH ₂	H, H	H, H	CO	541.5	542	61
151	H	4-CF ₃ -Ph	H	3,5-diCF ₃ -phenylCH ₂	H, H	H, H	CO	609.5	610	41
152	H	4-CF ₃ -Ph	H	4-Me-phenylCH ₂	H, H	H, H	CO	487.6	488	41
153	H	4-CF ₃ -Ph	H	Ph ₂ CH	H, H	H, H	CO	549.6	550	69
154	H	4-CF ₃ -Ph	H	4-NO ₂ -phenylCH ₂	H, H	H, H	CO	518.5	519	34
155	H	4-CF ₃ -Ph	H	4-(Me ₂ N)-phenylCH ₂	H, H	H, H	CO	516.6	517	29
156	H	4-CF ₃ -Ph	H	4-biphenylCH ₂	H, H	H, H	CO	549.6	550	19
157	H	4-CF ₃ -Ph	H	2-naphthylCH ₂	H, H	H, H	CO	523.6	524	10
158	H	4-CF ₃ -Ph	H	5-Cl-3-Me-benzo- thiopheneCH ₂	H, H	H, H	CO	578.1	578, 580	16
159	H	4-CF ₃ -Ph	H	4-(Me ₂ N)-phenyl(CH) ₂	H, H	H, H	CO	528.6	529	12
160	H	4-CF ₃ -Ph	H	3,5-diCF ₃ -phenyl	H, H	H, H	CO	595.5	596	10
161	H	4-I-Ph	H	2-Cl-phenylCH ₂	H, H	H, H	CO	565.9	566, 568	42
162	H	4-I-Ph	H	4-Cl-phenylCH ₂	H, H	H, H	CO	565.9	566, 568	30
163	H	4-I-Ph	H	3,4-diCl-phenylCH ₂	H, H	H, H	CO	600.3	600	44
164	H	4-I-Ph	H	2-F-phenylCH ₂	H, H	H, H	CO	549.4	550	40
165	H	4-I-Ph	H	4-F-phenylCH ₂	H, H	H, H	CO	549.4	550	79
166	H	4-I-Ph	H	4-CF ₃ -phenylCH ₂	H, H	H, H	CO	599.4	600	46
167	H	4-I-Ph	H	3,5-diCF ₃ -phenylCH ₂	H, H	H, H	CO	667.4	668	63
168	H	4-I-Ph	H	2-MeO-phenylCH ₂	H, H	H, H	CO	561.5	562	32
169	H	4-I-Ph	H	3-MeO-phenylCH ₂	H, H	H, H	CO	561.5	562	45
170	H	4-I-Ph	H	4-MeO-phenylCH ₂	H, H	H, H	CO	561.5	562	25
171	H	4-I-Ph	H	3,5-diMeO-phenylCH ₂	H, H	H, H	CO	591.5	592	25
172	H	4-I-Ph	H	2-Cl-phenyl	H, H	H, H	CO	551.9	552	32
173	H	4-I-Ph	H	4-Cl-phenyl	H, H	H, H	CO	551.9	552	72
174	H	4-I-Ph	H	3,4-diCl-phenyl	H, H	H, H	CO	586.3	587	50

16h

175	H	4-I-Ph	H	2-F-phenyl	H, H	H, H	CO	535.4	536	65
176	H	4-I-Ph	H	4-F-phenyl	H, H	H, H	CO	535.4	536	68
177	H	4-I-Ph	H	4-CF ₃ -phenyl	H, H	H, H	CO	585.4	586	53
178	H	4-I-Ph	H	3,5-diCF ₃ -phenyl	H, H	H, H	CO	653.4	654	53
179	H	4-I-Ph	H	2-thiophene	H, H	H, H	CO	523.4	524	53
180	H	4-I-Ph	H	5-Me-2-thiophene	H, H	H, H	CO	537.5	538	57
181	H	4-I-Ph	H	2-MeO-phenyl	H, H	H, H	CO	547.4	548	41
182	H	4-I-Ph	H	3-MeO-phenyl	H, H	H, H	CO	547.4	548	15
183	H	4-I-Ph	H	3,5-diMeO-phenyl	H, H	H, H	CO	577.5	578	42

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upon a square cm of skin surface, from about 2 $\mu\text{l}/\text{cm}^2$ to about 8 $\mu\text{l}/\text{cm}^2$ of topically active agent is present when amelioration of an inflammatory condition is desired.

The following examples are merely illustrative of the compounds, methods of making said compounds, compositions and methods of using said compounds and compositions, and do not serve to limit the scope of this invention.

Example 1

2,3,3-Triphenylpropionitrile, (Hauser, C.R. et al., Formation and Preferential β -Alkylation of the Dicarbanion of 2,3,3-Triphenylpropionitrile by Means of Potassium Amide in Liquid Ammonia. *J. Amer. Chem. Soc.*, 1959, 81, 4099-4102) was made as follows. A solution of phenylacetonitrile (1.00g, 0.0086 mol) and THF (17mL) was cooled to -78°C in a dry ice-acetone bath and treated dropwise with a solution of n-butyllithium in hexane (3.80 mL, 0.0095 mol). After stirring for 45 minutes at -78°C , a solution of diphenyl methylchloride (1.75 g, 0.0086 mol) and THF was added dropwise to give a light yellow solution. After stirring at room temperature overnight, water (20 mL) and diethyl ether (50 mL) were added with vigorous stirring. The organic layer was separated, dried over anhydrous magnesium sulfate (MgSO_4), filtered, and evaporated to give an oil. This material was triturated and filtered to give 1,2,2-triphenylpropionitrile.

Example 2

9H-(Fluoren-9-yl)phenylacetonitrile was prepared using the same procedure as that described in Example 1, however, 9-bromofluorene was substituted for diphenylmethylchloride. 9H-(Fluoren-9-yl)phenylacetonitrile was obtained, having a melting point of $146-148.3^\circ\text{C}$.

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Example 3

(10,11-Dihydro-5H-dibenzo[1,d]cyclohepten-4-yl)phenylacetonitrile was made using the same procedure as described above in Example 1, with the exception that 5-chloro-10,11-dihydro-5-H-dibenzo[a,d]cycloheptene was substituted for diphenylmethylchloride. (10,11-Dihydro-5H-dibenzo[1,d]cyclohepten-4-yl)phenylacetonitrile was obtained, having a melting point of 134.1-147.7°C.

Example 4

2-(4-Chlorophenyl)-3,3-diphenylpropionitrile was made using the same procedure as described for Example 1, but substituting 4-chlorophenylacetonitrile for phenylacetonitrile. The compound obtained had a melting point of 115.1-115.6°C.

Example 5

2-(2-Thienyl)-3,3-diphenylpropionitrile was made using the following procedure. To a mixture of 2-thiophenacetonitrile (16.30 g, 0.081 mol), benzyltriethylammonium chloride (0.185 g, 0.900081 mol), and 50% sodium hydroxide, diphenylmethylchloride (10.00 g, 0.081 mol) was added dropwise. this mixture was stirred for two hours at room temperature, heated at 40°C for 30 minutes and then was treated with benzaldehyde (0.18 g, 0.0017 mol). The reaction mixture was poured into an ice-water mixture (200 ml) and extracted twice with dichloromethane. The organic layers were combined, washed with 2N hydrochloric acid (100 ml), water (100 ml), and saturated sodium chloride solution (100 ml), dried over magnesium sulfate, filtered and evaporated. The residue was chromatographed on flash silica to give a solid which was recrystallized three times from ethanol affording 17.45 g (74.3%) of 2-(2-Thienyl)-3,3-diphenylpropionitrile as a crystalline solid, having a melting point of 102.7 - 105.3 °C.

Example 6

3,3-Bis-(4-fluorophenyl)-2-phenylpropionitrile was made using the same procedure as described in Example 5, but substituting phenylacetonitrile for 2-thiopheneacetonitrile and chlorobis(4-fluorophenyl)methane for diphenylmethylchloride. The end product had a melting point of 142.5-143.8°C.

Example 7

2-(4-Iodophenyl)-3,3-diphenylpropionitrile was made using the same procedure as described in Example 5, but substituting 4-iodophenylacetonitrile for 2-thiopheneacetonitrile.

Example 8

1,2,2-Triphenylcyclopropyl nitrile was made using the procedure of C. R. Hauser, T. M. Harris, and T. G. Ledford [*J. Amer. Chem. Soc.*, 1959, 81, 4099-4102]. A solution of KNH_2 and liquid NH_3 was made by adding potassium (24.5 g, 0.63 mol) to liquid NH_3 (1500 ml). 2,3,3-triphenylpropionitrile (87.5 g, 0.31 mol) was slowly added to the KNH_2/NH_3 solution. After stirring for 10 minutes, this mixture was treated with a solution of dichloromethane (31.5 g, 0.37 mol) and diethyl ether (150 ml). After 1.5 hour, another portion of dichloromethane (6.0 g, 0.071 mol) and diethyl ether (25.0 ml) was added and the reaction mixture stirred for another hour at -78°C. Diethyl ether was added and the NH_3 was allowed to evaporate. The ethereal solution was washed with water, 2N hydrochloric acid and water. The organic layer was separated, dried over potassium carbonate, filtered and evaporated to a solid residue. This material was recrystallized twice from methanol affording 47.0 g (51%) of 1,2,2-Triphenylcyclopropyl nitrile as a crystalline solid.

Example 9

2,3,3-Triphenylpropylamine was made according to the following procedure. A solution of 2,3,3-triphenylpropionitrile (10.00 g, 0.035 mol) and THF (80

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ml) was added dropwise to a solution of LiAlH_4 (3.40 g, 0.089 mol) in THF (100 ml) at 0°C . The resulting mixture was stirred for 24 hours at room temperature and then refluxed for 24 hours. After cooling in an ice bath, the reaction mixture was treated with water (3.40 ml), 3N sodium hydroxide (10.20 ml) and water (3.4 ml) followed by the addition of magnesium sulfate.

The mixture was filtered and the filtrate was evaporated to an oil. This material was dissolved in diethyl ether (30 ml) and diethyl ether/anhydrous hydrochloric acid (25 ml, 0.025 mol) was added. A white solid was filtered and partitioned between diethyl ether and 3N sodium hydroxide. The organic layer was separated, dried over potassium carbonate, filtered, and evaporated affording 2,3,3-Triphenylpropylamine as a crystalline solid.

Example 10

2-(4-Chlorophenyl)-3,3-diphenylpropylamine was made using the same procedure as described in Example 9, but substituting 2-(4-Chlorophenyl)-3,3-diphenylpropionitrile for 2,3,3-triphenylpropionitrile. The end product had a melting point of $104.1\text{--}105.7^\circ\text{C}$.

Example 11

2-(9H-[Fluoren-9-yl])-2-(phenyl)ethylamine was made using the procedure as set forth in Example 9, but substituting 9H-(Fluoren-9-yl)phenylacetonitrile for 2,3,3-triphenylpropionitrile and diethyl ether for THF. An oil was obtained.

Example 12

3,3-Bis-(4-fluorophenyl)-2-(phenyl)propylamine was made using the procedure as set forth in Example 9, but substituting 3,3-bis-(4-fluorophenyl)-2-phenylpropionitrile for 2,3,3-triphenylpropionitrile and diethyl ether for THF. The endproduct was a white solid.

Example 13

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3,3-Diphenyl-2-(2-thienyl)propylamine was made using the procedure as set forth in Example 9, but substituting 2-(2-Thienyl)-3,3-diphenylprionitrile for 2,3,3-triphenylpropionitrile and diethyl ether for THF. The end product was a beige solid having a melting point greater than 200°C (decomposition).

5 Example 14

1,2,2-triphenylcyclopropylmethylamine was made using the procedure as set forth in Example 9, but substituting 1,2,2-Triphenylcyclopropylnitrile for 2,3,3-triphenylpropionitrile and diethyl ether for THF. The end product was a white solid.

10 Example 15

2-(4-Iodophenyl)-3,3-diphenylpropylamine was made using the following procedure. A solution of TFA (3.30 g, 0.030 mol) and THF (10 ml) was slowly added to a slurry of sodium borohydrate (1.10 g, 0.029 mol) and THF (20 ml) at room temperature. After gas evolution ceased, the reaction was stirred for fifteen minutes and then treated dropwise with a solution of 2-(4-Iodophenyl)-3,3-diphenylpropionitrile (4.87 g, 0.012 mol) and THF (20 ml). After stirring overnight at room temperature, water was added slowly followed by dichloromethane (40 ml). The organic layer was dried over potassium carbonate, filtered and evaporated to an oil. This material was dissolved in diethyl ether and treated with anhydrous hydrochloric acid/diethyl ether (10 ml). A white solid was filtered and partitioned between dichloromethane and 3N sodium hydroxide. The organic layer was separated, dried over potassium carbonate, filtered and evaporated to give 2-(4-Iodophenyl)-3,3-diphenylpropylamine as a solid.

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Example 16

2-(10,11-Dihydro-5H-dibenzo[1,d]cyclohepten-4-yl)-2-(phenyl)ethylamine was made as follows. A solution of 1M BH_3 -THF (24 ml, 0.024 mol) at room temperature was treated with a solution of (10,11-Dihydro-5H-dibenzo[1,d]cyclohepten-4-yl)phenylacetonitrile (5.0 g, 0.016 mol) and THF (70 ml). The resulting solution was refluxed for 2 hours, cooled to 0°C and treated with methanol (50 ml) followed by 6N hydrochloric acid (125 ml). The mixture was heated at 70°C for 1 hour, cooled to 0°C, adjusted to pH 12 with 50% sodium hydroxide solution, and extracted two times with ethylacetate. The organic layers were combined, dried, filtered, and evaporated to a yellow oil. This material was triturated with hexane and filtered. The filtrate was evaporated and the residue was chromatographed on flash silica using ethylacetate:hexane (8:2) as the eluant to give a 2.29 g (46%) yield of 2-(10,11-Dihydro-5H-dibenzo[1,d]cyclohepten-4-yl)-2-(phenyl)ethylamine as an oil.

Example 17

Compound 29 was made in accordance with the following procedure. A solution of thiopheneacetyl chloride (0.281 g, 0.0017 mol) and ethylene dichloride (8.0 ml) was added slowly to an ice-cooled mixture of 2,3,3-Triphenylpropylamine (0.50 g, 0.0017 mol), sodium acetate (0.18 g, 0.0022 mol) and ethylene chloride (8.0 ml). After stirring overnight at room temperature, water was added with thorough mixing. The resulting organic layer was separated, washed successively with 1N sodium hydroxide solution and 1N hydrochloric acid solution, dried over magnesium sulfate, filtered and evaporated to an oil which solidified. Two recrystallizations of this material afforded 0.410 g (59%) of 29 as a crystalline solid, having a melting point of 130-132 °C

Example 18

Other compounds may be obtained in accordance with the procedure set forth in Example 17, requiring the substitution for thiopheneacetyl chloride or 2,3,3-Triphenylpropylamine, such as compounds: 1, 6, 7, 18, 29, 78, 79, and 82.

Example 19

Compound 80 was made using the following procedure: A solution of 2-chlorophenylacetic acid (0.289 g, 0.0017 mol), 1,1'-carbonyldiimidazole (0.271 g, 0.0017 mol) and acetonitrile (25 ml) was stirred for twenty minutes at room temperature and treated with 1,2,2-triphenylcyclopropylmethylamine (0.500 g, 0.0017 mol). After stirring for 24 hours, the reaction was evaporated and the residue dissolved in methylene dichloride. This solution was washed with water (10 ml), 1N HCl (10 ml), and water (10 ml). The organic layer was separated, dried over magnesium sulfate, filtered, and evaporated to an oil. This material was dissolved in ethylene dichloride and diethyl ether was added causing a crystalline solid to form. Filtration afforded 0.501 g (65%) of 80 as a crystalline solid with a melting point of 128.5 - 130.5 °C.

Example 20

Following the procedure of Example 19, substituting for the 2-chlorophenylacetic acid or 1,2,2-triphenylcyclopropylmethylamine equivalent amounts of the appropriate starting materials and substituting ethylene dichloride for the acetonitrile used therein, the following compounds may be obtained: 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 19, 20, 21, 22, 24, 25, 26, 27, 28, 30, 34, 37, 38, 39, 40, 41, 42, 43, 45, 46, 48, 49, 61, 62, 63, 64, 81, 83, 84, 85, 86, 87, 88, 89, and 90.

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Example 21

Compound 66 was made as follows: A solution of phenyl acetic acid (0.30 g, 0.0024 mol), 2-(9H-[Fluoren-9-yl])-2-(phenyl)ethylamine (0.70 g, 0.0024 mol), and ethylene dichloride (10 ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.55 g, 0.0029 mol). After stirring overnight, the reaction solution was washed with 3N sodium hydroxide, 6N HCl and saturated NaCl solution. The organic layer was separated, dried over magnesium sulfate and evaporated to a semi-solid. This material was triturated with diethyl ether and filtered to give a solid which was recrystallized from methanol affording 0.12 g (12%) of Compound 66 as a white crystalline solid having a melting point of 148.7 - 150.8 °C.

Example 22

Following the procedure of Example 21, substituting for the phenylacetic acid or 2-(9H-[Fluoren-9-yl])-2-(phenyl)ethylamine equivalent amounts of the appropriate starting materials, the following compounds may be obtained: 15, 16, 17, 23, 31, 32, 44, 65, 67, 68, 69, 70, 71, 72, 74, 75, 76, 77, and 91.

Example 23

Compound 52 was made in accordance with the following procedure: A solution of 2,3,3-Triphenylpropylamine (0.25 g, 0.0009 mol) and methylene dichloride (25 ml) was treated with 2-chlorophenyl isocyanate (0.13 g, 0.0009 mol) at room temperature. A solid formed which was filtered and recrystallized from methanol-hexane to give 0.14 g (75%) of 52 as a white crystalline solid having a melting point of 210-211 °C.

Example 24

Following the procedure of Example 23, substituting for the chlorophenyl isocyanate or 2,3,3-Triphenylpropylamine used therein, equivalent amounts of the appropriate starting materials, the following compounds may be obtained: 50, 51, 53, 54, 55, 92, 93, 94, and 95

Example 25

Compound 40 was made as follows: An ice-cooled solution of 2,3,3-triphenylpropylamine (0.674 g, 0.0024 mol) and CHCl_3 (20 ml) was treated with 2-thiophenesulfonyl chloride (0.475 g, 0.0026 mol) followed by diisopropylethylamine (0.764 g, 0.0059 mol) and stirred at room temperature overnight. The reaction was washed with 1N HCl (20 ml) and saturated NaCl solution. The organic layer was separated, dried over magnesium sulfate, filtered and evaporated affording 0.660 g (66%) of 40 as a solid having a melting point of 169-170.9 °C.

Example 26

Following the procedure of Example 25, substituting for the 2,3,3-Triphenylpropylamine used therein an equivalent amount of 2-(4-chlorophenyl)-3,3-diphenylpropylamine, compound 41 may be obtained.

Example 27

Compound 57 was made in accordance with the following procedure: To a solution of 2,3,3-Triphenylpropylamine (0.25 g, 0.0009 mol), triethylamine (0.09 g, 0.0009 mol) and CHCl_3 (25 ml) was added 4-fluorophenyl chloroformate (0.2 g, 0.0009 mol) and the resulting solution was stirred for 45 minutes. The reaction was then washed with 1N HCl, and brine. The

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organic layer was separated, dried over magnesium sulfate, filtered and evaporated to white solid. This material was recrystallized from methanol/hexane to give 0.15 g (39%) of 57 as a white crystalline solid having a melting point of 150-151 °C.

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Example 28

Following the procedure of Example 27, but substituting for the 2,3,3-Triphenylpropylamine and 4-fluorophenyl chloroformate used therein, equivalent amounts of the appropriate starting materials, the following compounds may be obtained: 56, 58, 59, 96, and 97.

10

Example 29

Compound 17 was made as follows: A mixture of N-[3,3-bis-(4-fluorophenyl)-2-phenylpropyl]-2-phenylacetamide [Compound 18] (0.84 g, 0.0019 mol), dimethylsulfate (0.37 g, 0.0029 mol), benzyltriethylammonium chloride (0.14 g, 0.00075 mol), 50% NaOH (30 ml) was stirred overnight at room temperature. Water was added and the mixture was extracted with ethylene dichloride. The organic layer was separated, dried over potassium carbonate, filtered and evaporated to an oil which was crystallized from diethyl ether-hexane affording 0.080 g (9%) of 17 as a yellow crystalline solid having a melting point of 86.9-88.2 °C.

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Example 30

Compound 98 was prepared as follows: A mixture of 2-(3,4-methylenedioxyphenyl)-3,3-diphenylpropylamine (18.0 g, 0.055 mol) and anhydrous THF (120 mL) at -70° C. was treated dropwise with a 1.0M solution of DiBAL (100 mL, 0.110 mol). The reaction was stirred for 1 hour at -70° C and then at 25° C for 1.5 hours. The reaction was cooled to 0° C and treated with ethanol (20 mL) followed by 10% aqueous HCl (150 mL).

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Extraction with ethyl acetate, drying over anhydrous MgSO_4 , evaporation and purification by flash chromatography (silica gel) afforded 2-(3,4-methylenedioxyphenyl)-3,3-diphenylpropionaldehyde a solid. A mixture of this material (8.0 g, 0.024 mol), Rink amine resin (8.73 g, 0.0044 mol), and trimethylorthoformate (60 mL) was shaken for 4 days, filtered and washed twice with trimethylorthoformate, methylene chloride, and dichloroethane. The resulting resin was shaken with $\text{NaBH}(\text{Oac})_3$ (4.63 g, 0.022 mol), acetic acid (1.83 mL) and dichloroethane (60 mL) for two days. The resulting resin was washed with methanol, methylene chloride, 10% acetic acid/methylene chloride, 10% triethylamine/methylene chloride, methylene chloride, and methanol. This resin (0.235 g, 0.0001 mol) was shaken for 2 days with HATU (0.090 g, 0.00024 mol), diisopropylethylamine, (175 μL), 4-chlorophenylacetic acid (0.085 g, 0.0005 mol), and DMF (2 mL). The resin was filtered and washed three times each with DMF, methylene chloride, and methanol and dried. The dried resin was treated with 10% TFA/methylene chloride and filtered. The filtrate was blown dry with nitrogen to afford 0.042 g (87%) of compound 98, electrospray mass spectrometry m/e = 484.

Example 31

Following the procedure of Example 30, but substituting for the 4-chlorophenylacetic acid and 2-(3,4-methylenedioxyphenyl)-3,3-diphenylpropylamine used therein, equivalent amounts of the appropriate starting materials, the following compounds may be obtained: 99-161, 164, 168, 173, 174, 176-178, 180, and 182.

Example 32

Compound 162 was prepared as follows: A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (7.67 g, 0.040 mol) and methylene chloride (300 mL) was washed with 10% NH_4OH , dried over

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MgSO₄, filtered and evaporated. The residue was dissolved in DMF (100 mL) and mixed with Merrifield resin (20.0 g, 0.020 mol) at 100° C overnight. The mixture was filtered and the resin was washed with DMF, methanol, and methylene chloride. A mixture of this resin (0.48 g, 0.00048 mol), 4-chlorophenylacetic acid (0.0205 g, 0.00012 mol), 2(4-iodophenyl)-3,3-diphenylpropylamine (0.0413 g, 0.0001 mol), and CHCl₃ (2.0 mL) was agitated for 2 days, filtered, and washed with CHCl₃. The filtrate was blown dry with nitrogen affording compound 163, 0.0425g. (88%), CI mass spectrometry m/e = 483.99.

Example 33

Following the procedure of Example 32, but substituting for the 4-chlorophenylacetic acid used therein, equivalent amounts of the appropriate starting materials, the following compounds may be obtained: 163, 165-167, 169-172, 175, 179, 181, and 183.

Example 34

A human glucocorticoid receptor binding assay was carried out to determine the extent to which the compounds of this invention have the ability to bind to human glucocorticoid receptors. This binding ability may be indicative of the antiinflammatory activity of the compound. The test was carried out as follows.

Human glucocorticoid receptors were prepared from either insect cells (Sf21) infected with baculovirus hGR or from a lymphoblast cell line which expresses high levels of endogenous hGR (IM9). The receptor binding reactions, with or without test compounds, were set up in 96-well microtiter plates which were previously siliconized with SIGMACOTE™, a chlorinated organopolysiloxane in heptane. The binding components, 3(H) Triamcinolone acetonide (TAA), glycerol/molybdate-containing buffer and unlabeled compounds were added to the wells using a combination of

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BIOMEK laboratory automation system and repeat pipettes. After four hours of incubation, the samples were precipitated with polyethylene glycol and filtered through Whatman GF/F paper using a TOMTEK cell harvester. The filter mate with 96 samples were bound to a solid-phase scintillant and directly counted in a BETAPLATE counter. The IC_{50} values were determined based on competition of 3H TAA with the test compounds at 6-8 concentrations ranging from 10^{-10} - 10^{-5} M and calculated using the Chung-Prusoff equation. The activity of test compounds to displace $3(H)$ TAA binding to hGR is also expressed as percent inhibition at 1 μM . The results of this test are set forth in Table 1 below.

Example 35

A human progesterone receptor binding assay was performed in order to determine selectivity of the compounds, as follows. Human progesterone receptors were prepared from either insect cells (SF21) infected with baculovirus hPR A, or from a breast cancer cell line, T47D, which expresses high levels of endogenous hPR. The receptor binding reactions, with or without test compounds, were set up in 96-well microtiter plates which were previously siliconized with SIGMACOTE. The binding components, $3(H)$ R5020 Promegestone, a high affinity ligand for the progesterone receptors, glycerol/molybdate-containing buffer and unlabeled compounds were added to the wells using a combination of BIOMEK laboratory automation system and repeat pipettes. After overnight incubation, the samples were precipitated with polyethylene glycol and filtered through Whatman GF/F paper using a TOMTEK cell harvester. The filter mate with 96 samples were bound to a solid-phase scintillant and directly counted in the BETAPLATE counter. Only those compounds that were active in the human glucocorticoid receptor assay set forth in Example

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30 were used for progesterone receptor binding to determine cross-reactivity profiles, if any. The activity of test compounds to displace 3(H) R5020 binding to hPR is expressed as percent inhibition at the two concentrations, 10^{-6} and 10^{-5} Molar. Those compounds that do not inhibit 3(H) TAA binding by 50% at 10^{-5} M were not considered active. Surprisingly, the compounds of this invention selectively bind to the hGR but show little or no affinity for the hPR.

Example 36

Several triphenylpropanamide compounds of this invention, having varying affinities for the human glucocorticoid receptor, were tested for topical antiinflammatory activity in mouse ear inflammation models. Compounds with low receptor affinity ($IC_{50} > 20$ nM) were weakly active or inactive at reducing ear inflammation induced by the contact sensitizer oxazolone. Compounds having receptor affinities closer to hydrocortisone were as nearly active as hydrocortisone in suppressing mouse oxazolone-induced contact hypersensitization (MOCH) and phorbol ester-induced ear edema. The *in vivo* studies of this example were conducted as follows.

Albino male CD-1 mice, 7-9 weeks old were used in this example. A 0.005% (w/v) TPA or 20% (w/v) arachidonic acid (AA) solution was made in acetone. A 20 μ l volume of the TPA or AA was applied to the dorsal left ear of the mouse. Compounds of this invention were placed in a composition containing ethanol/propylene glycol at a ratio of 70:30 were applied to the left ear of each mouse in an amount of 20 μ l immediately after application of the TPA or AA. The right ear was not treated. The mice were sacrificed by carbon dioxide inhalation 5.5 hours after administration of TPA and one hour after administration of AA, the left and right ears were removed and a 7 mm

biopsy was removed from each ear and weighed. The difference in biopsy weights between the right and left ears was calculated. Antiinflammatory effects of compounds were evident as an inhibition of the increase in ear weight.

5 In determining the MOCH using the compounds of this invention, albino male CD-1 mice, 7-9 weeks old were induced on the shaved abdomen with 50 μ l of 3% oxazolone in acetone/corn oil (Day 0). On Day 5, a 20 μ l volume of 2% oxazolone in acetone was applied to the dorsal left ear of the mouse. Compounds (made in ethanol/propylene glycol, 70:30) were
10 applied to the left ear in 20 μ l volume, one hour after oxazolone challenge. The right ear was not treated. The mice were sacrificed by carbon dioxide inhalation 24 hours after oxazolone challenge, the left and right ears were removed and a 7 mm biopsy was removed from each ear and weighed. The difference in biopsy weights between the right and left ears was calculated.
15 Antiinflammatory effects of compounds were evident as an inhibition of the increase in ear weight.

The results of the foregoing *in vivo* testing is set forth in the following Table 2:

Table 2

Compound No.	Oxazolone Ear Swelling (MOCH)
	% inhibition vs. Vehicle at 1 mg
2	4
4	1
5	13
6	38
9	18
10	19

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	11	33
	12	36
	13	10
	14	11
5	15	47
	16	46
	19	2
	20	32
	22	15
10	23	41
	24	21
	25	9
	26	-5
	27	20
15	28	28
	29	83
	30	21
	31	14
	32	83
20	33	74
	34	29
	35	36
	36	13
	37	25
25	38	13
	39	24
	40	15
	41	3

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	42	27
	43	47
	44	3
	45	31
5	46	4
	47	51
	48	22
	49	20
	50	30
10	53	24
	54	10
	55	18
	56	38
	57	13
15	58	16
	60	27
	61	17
	62	36
	63	3
20	64	26
	65	13
	66	20
	68	28
	69	43
25	72	50
	74	18
	75	26
	76	23

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	77	41
	79	18
	80	54
	81	22
5	82	23
	83	4
	84	54
	85	16
	87	22
10	88	29
	89	16
	90	65
	91	13
	92	42
15	93	26
	94	35
	95	16
	96	52
	97	50
20	98	85
	hydrocortisone	75-85

In accordance with the foregoing table, for example, compounds 23, 15, and
 16 had moderate topical activity whereas compounds 29, 32, and 98 were
 25 equiactive with hydrocortisone. Compounds 29 and 32 were tested for
 dose-related activity in the oxazolone model. As shown below in Table 3,
 both compounds inhibited ear swelling in a dose-dependent manner.

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Table 3

Treatment Dose (%)		Oxazolone Ear Swelling % Experiment 1	Inhibition vs. Vehicle Experiment 2
Hydrocortisone	1	78.9	58.2
Compound 29	3	66.5	---
		49.9	---
	1	34.7	---
	0.3	4.3	---
	0.1		
Compound 32	3	---	36.5
		---	31.45
	1	---	18.95
	0.3	---	11.2
	0.1		

Both compounds were also tested in a TPA-induced ear edema model, which also shows effect of glucocorticoids. At equivalent doses, the two non-steroidal compounds were only slightly less active than hydrocortisone, as set forth in Table 4 below.

Table 4

Treatment	Dose (%)	% Inhibition of TPA Ear Edema vs. Vehicle
Hydrocortisone	1	80.6
Compound 29	1	64.9
Compound 32	1	60.0

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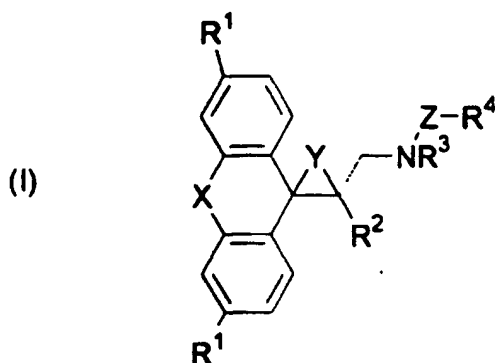
These tests demonstrate that the compounds of this invention (triphenylpropanamides) are topically active as antiinflammatory agents. Because of their selective effects on transcription factors, they should not cause the side effects known to be associated with classical glucocorticoids. In addition to inflammation, the triphenylpropanamides of this invention may be useful as therapeutics in other glucocorticoid-responsive skin conditions.

5

WHAT IS CLAIMED IS:

1. A compound having the formula:

5



wherein **X** is a single bond, hydrogen, sulfur or NR⁶, (CH₂)_n wherein n is an integer from 1 to 3; -HC=CH-; and -CH_xW wherein W may be oxygen, sulfur or NR⁶;

R¹ is from one to three substituent groups each selected from the group consisting of lower alkyl (C₂ - C₆), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

R² is a phenyl group in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl (C₂ - C₆), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile, a heteroaromatic ring selected from the group consisting of substituted- or unsubstituted thiophene, furan, pyrrole, or pyridine;

Y is -CH₂- or hydrogen;

R³ is chosen from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl in which said phenyl group is substituted with hydrogen

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or from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone;

R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted- or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted- or unsubstituted thiophene, furan, pyrrole or pyridine; and

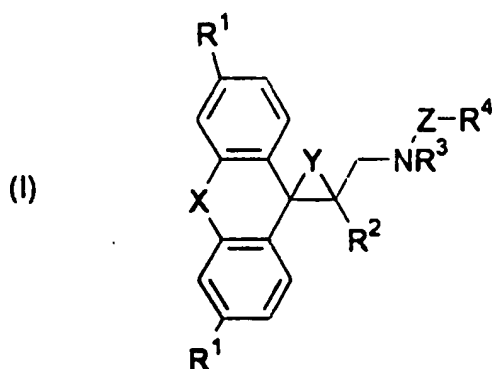
R⁵ is selected from the group consisting of: hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl, in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl (C₂ - C₆), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido, or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile.

2. A compound according to claim 1 wherein **R¹** is selected from the group consisting of hydrogen and halo group.

3. A compound according to claim 2 wherein **R¹** is hydrogen.

4. A compound according to claim 2 wherein R^1 is halogen.
5. A compound according to claim 4 wherein R^1 is fluorine.
6. A compound according to claim 1 wherein X is hydrogen.
7. A compound according to claim 1 wherein Y is hydrogen.
- 5 8. A compound according to claim 1 wherein R^2 is selected from the group consisting of phenyl and halophenyl.
9. A compound according to claim 8 wherein R^2 is phenyl.
10. A compound according to claim 8 wherein R^2 is halophenyl.
11. A compound according to claim 10 wherein R^2 is chlorophenyl.
- 10 12. A compound according to claim 1 wherein R^3 is selected from the group consisting of hydrogen and lower alkyl.
13. A compound according to claim 12 wherein R^3 is hydrogen.
14. A compound according to claim 1 wherein R^4 is selected from the group consisting of straight-chain alkyl, phenyllower alkyl and heteroaromatic lower
15 alkyl.
15. A compound according to claim 14 wherein R^4 is heteroaromatic lower alkyl.
16. A compound according to claim 15 wherein R^4 is thiophene.
17. A compound according to claim 1 wherein Z is carbonyl.
- 20 18. A compound having the formula:

- 40 -



5

wherein X is hydrogen;

R^1 is selected from the group consisting of hydrogen and halogen

10

group;

R^2 is a phenyl group in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile, a heteroaromatic ring selected from the group consisting of substituted- or unsubstituted thiophene, furan, pyrrole, or pyridine;

15

Y is hydrogen;

R^3 is chosen from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; phenyl lower alkyl in which said phenyl

20

group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone; and

R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted- or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted- or unsubstituted thiophene, furan, pyrrole or pyridine.

19. A compound according to claim 18 wherein **R¹** is hydrogen.

20. A compound according to claim 18 wherein **R¹** is halogen.

21. A compound according to claim 20 wherein **R¹** is fluorine.

22. A compound according to claim 18 wherein **R²** is selected from the group consisting of phenyl, halophenyl and thio.

23. A compound according to claim 22 wherein **R²** is phenyl.

24. A compound according to claim 23 wherein **R²** is halophenyl.

25. A compound according to claim 24 wherein **R²** is chlorophenyl.

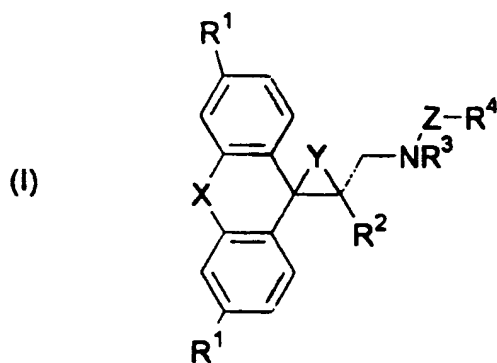
26. A compound according to claim 18 wherein **R³** is selected from the group consisting of hydrogen and lower alkyl.

27. A compound according to claim 26 wherein **R³** is hydrogen.

28. A compound according to claim 18 wherein **R⁴** is selected from the group consisting of straight-chain alkyl, phenyllower alkyl and heteroaromatic lower alkyl.

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29. A compound according to claim 28 wherein R^4 is heteroaromatic lower alkyl.
30. A compound according to claim 29 wherein R^4 is thiophene.
31. A compound having the formula:



wherein X is hydrogen;

Y is hydrogen;

R^1 is selected from hydrogen and halogen;

R^2 is selected from phenyl and halophenyl;

R^3 is chosen from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy,

amino, amido, sulfonamido or nitrile; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

5 Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone; and

 R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group
10 consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted- or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted- or unsubstituted thiophene, furan, pyrrole or pyridine.

15 32. A compound according to claim 31 wherein R³ is selected from the group consisting of hydrogen and lower alkyl.

 33. A compound according to claim 32 wherein R³ is hydrogen.

 34. A compound according to claim 31 wherein R⁴ is selected from the group consisting of straight-chain alkyl, phenyllower alkyl and heteroaromatic
20 lower alkyl.

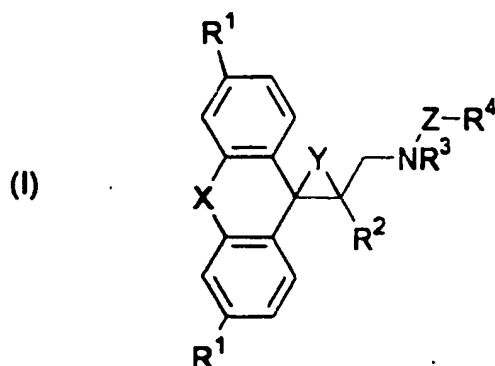
 35. A compound according to claim 34 wherein R⁴ is heteroaromatic lower alkyl.

 36. A compound according to claim 35 wherein R⁴ is thiophene.

 37. A compound according to claim 31 wherein Z is carbonyl.

25 38. A compound having the formula:

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5

wherein X is hydrogen;

Y is hydrogen;

10

R¹ is selected from hydrogen and halogen;

R² is selected from phenyl and halophenyl;

R³ is selected from hydrogen and lower alkyl;

Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone; and

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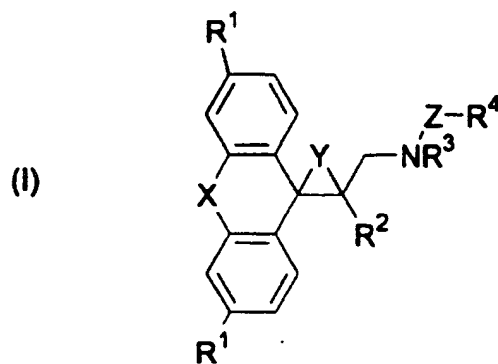
R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon

atoms; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted- or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted- or unsubstituted thiophene, furan, pyrrole or pyridine.

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39. A compound according to claim 38 wherein R^3 is hydrogen.
40. A compound according to claim 38 wherein R^3 is methyl.
41. A compound according to claim 38 wherein R^4 is selected from the group consisting of straight-chain alkyl, phenyl, lower alkyl and heteroaromatic lower alkyl.
42. A compound according to claim 41 wherein R^4 is heteroaromatic lower alkyl.
43. A compound according to claim 42 wherein R^4 is thiophene.
44. A compound according to claim 38 wherein Z is carbonyl.
45. A compound having the formula:



wherein X is hydrogen;

Y is hydrogen;

R^1 is selected from hydrogen and halogen;

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R^2 is selected from phenyl and halophenyl;

R^3 is selected from hydrogen and lower alkyl;

Z is carbonyl; and

R^4 is straight- or branched-chain alkyl having from 2 to 12 carbon

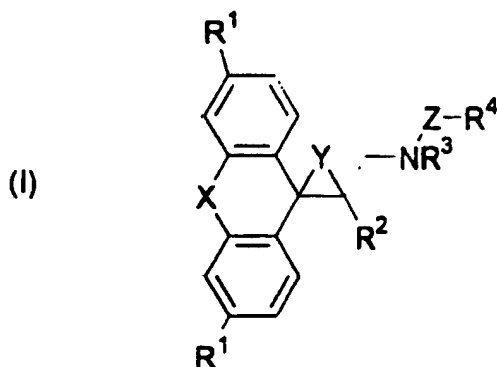
atoms; phenylloweralkyl in which said phenyl group is substituted with
hydrogen or with one to three substituent groups each selected from the group
consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy,
amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted-
or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring
connected by a lower alkyl chain wherein said heteroaromatic ring is chosen
from substituted-or unsubstituted thiophene, furan, pyrrole or pyridine.

46. A compound according to claim 45 wherein R^4 is selected from the
group consisting of straight-chain alkyl, phenyllower alkyl and heteroaromatic
lower alkyl.

47. A compound according to claim 46 wherein R^4 is heteroaromatic lower
alkyl.

48. A compound according to claim 47 wherein R^4 is thiophene.

49. An antiinflammatory composition comprising a pharmaceutically
acceptable carrier and an antiinflammatory-effective amount of a compound
having the formula:



wherein **X** is a single bond, hydrogen, sulfur or NR^5 , $(\text{CH}_2)_n$ wherein *n* is an integer from 1 to 3; $-\text{HC}=\text{CH}-$; and $-\text{CH}_2\text{W}$ wherein **W** may be oxygen, sulfur or NR^5 ;

R^1 is from one to three substituent groups each selected from the group consisting of lower alkyl ($\text{C}_2 - \text{C}_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

R^2 is a phenyl group in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($\text{C}_2 - \text{C}_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile, a heteroaromatic ring selected from the group consisting of substituted- or unsubstituted thiophene, furan, pyrrole, or pyridine;

Y is $-\text{CH}_2-$ or hydrogen;

R^3 is chosen from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each

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selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone;

5 R^4 is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted-
10 or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted-or unsubstituted thiophene, furan, pyrrole or pyridine; and

15 R^6 is selected from the group consisting of: hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl, in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido, or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with from one to three substituent groups each selected from the group consisting of lower alkyl,
20 lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile.

50. A composition according to claim 49 wherein R^1 is selected from the group consisting of hydrogen and halo group.

51. A compound according to claim 50 wherein R^1 is hydrogen.

25 52. A compound according to claim 50 wherein R^1 is halogen.

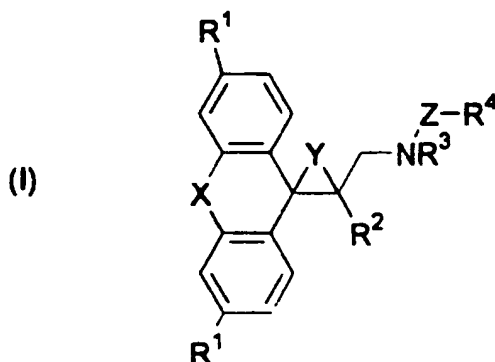
53. A compound according to claim 52 wherein R^1 is fluorine.

54. A compound according to claim 49 wherein X is hydrogen.

55. A compound according to claim 49 wherein Y is hydrogen.

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56. A compound according to claim 49 wherein R^2 is selected from the group consisting of phenyl and halophenyl.
57. A compound according to claim 56 wherein R^2 is phenyl.
58. A compound according to claim 57 wherein R^2 is halophenyl.
59. A compound according to claim 58 wherein R^2 is chlorophenyl.
60. A compound according to claim 49 wherein R^3 is selected from the group consisting of hydrogen and lower alkyl.
61. A compound according to claim 60 wherein R^3 is hydrogen.
62. A compound according to claim 49 wherein R^4 is selected from the group consisting of straight-chain alkyl, phenyllower alkyl and heteroaromatic lower alkyl.
63. A compound according to claim 62 wherein R^4 is heteroaromatic lower alkyl.
64. A compound according to claim 63 wherein R^4 is thiophene.
65. A compound according to claim 49 wherein Z is carbonyl.
66. A method of making a compound having the formula:



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wherein **X** is a single bond, hydrogen, sulfur or NR^6 , $(\text{CH}_2)_n$ wherein *n* is an integer from 1 to 3; $-\text{HC}=\text{CH}-$; and $-\text{CH}_x\text{W}$ wherein **W** may be oxygen, sulfur or NR^6 ;

R¹ is from one to three substituent groups each selected from the group consisting of lower alkyl ($\text{C}_2 - \text{C}_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

R² is a phenyl group in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($\text{C}_2 - \text{C}_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile, a heteroaromatic ring selected from the group consisting of substituted- or unsubstituted thiophene, furan, pyrrole, or pyridine;

Y is $-\text{CH}_2-$ or hydrogen;

R³ is chosen from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone;

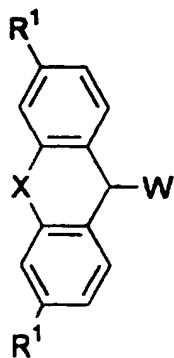
R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted-

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or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted or unsubstituted thiophene, furan, pyrrole or pyridine; and

R^6 is selected from the group consisting of: hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl, in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido, or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile comprising the steps of

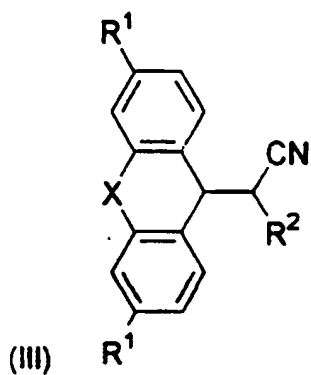
(1) reacting R^2CH_2CN with a compound having the formula (II) in the presence of $nBuLi$:



(II) $W = Cl, Br$

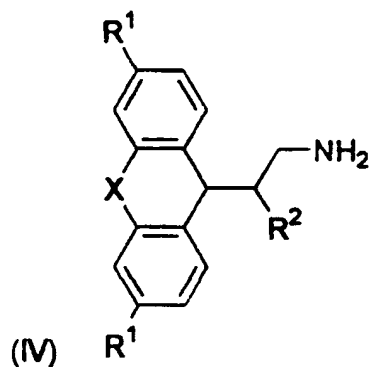
to obtain a compound having the formula (III)

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(2) reacting said compound of formula (III) with LAH to form a compound of formula (IV):

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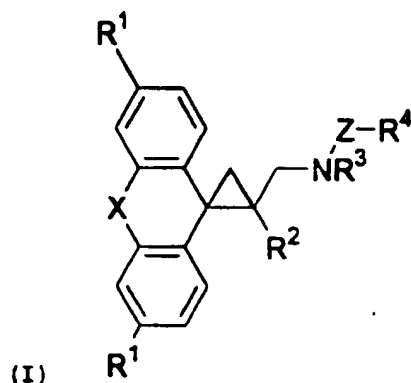
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and

(3) reacting said compound of formula (IV) with compound selected from the group consisting of: (a) sodium acetate and $R^4\text{COCl}$; (b) CDI and $R^4\text{CO}_2\text{H}$; (c) $\text{EtN}=\text{C}=\text{N}(\text{CH}_2)_3\text{NMe}_2 \cdot \text{HCl}$; (d) $R^4\text{CO}_2\text{H}$; (e) ClCO_2R^4 ; (f) $\text{ClC}=\text{O}(\text{NHR}^4)$; and (g) $R^4\text{SO}_2\text{Cl}$ to obtain a compound of formula (I).

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67. A method of making a compound having the formula:



wherein X is a single bond, hydrogen, sulfur or NR^6 , $(CH_2)_n$ wherein n is an integer from 1 to 3; $-HC=CH-$; and $-CH_xW$ wherein W may be oxygen, sulfur or NR^6 ;

10 R^1 is from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

15 R^2 is a phenyl group in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile, a heteroaromatic ring selected from the group consisting of substituted- or unsubstituted thiophene, furan, pyrrole, or pyridine;

20 R^3 is chosen from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group

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consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

Z is selected from the group consisting of carbonyl; carboxy, carbonylamino; or sulfone;

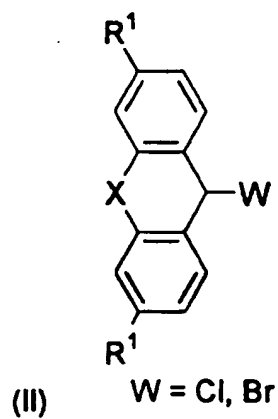
R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted- or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted-or unsubstituted thiophene, furan, pyrrole or pyridine; and

R⁵ is selected from the group consisting of: hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl, in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl (C₂ - C₆), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido, or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile comprising the steps of

(1) reacting R²CH₂CN with a compound having the formula (II) in the presence of nBuLi:

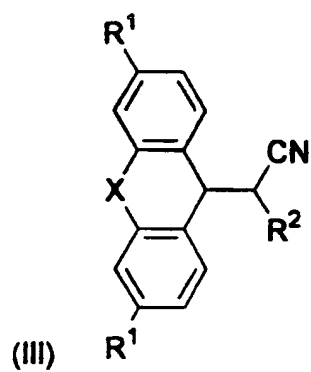
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to obtain a compound having the formula (III)

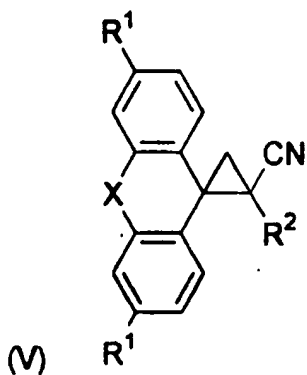
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(2) reacting said compound of formula (III) with CH_2Cl_2 in the presence of KNH_2 and liquid NH_3 to obtain a compound having formula (V):

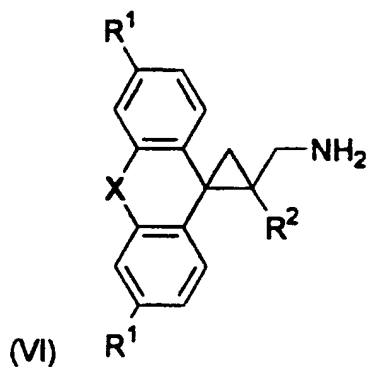
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(3) reacting said compound of formula (V) with LAH to form a compound of formula (VI):

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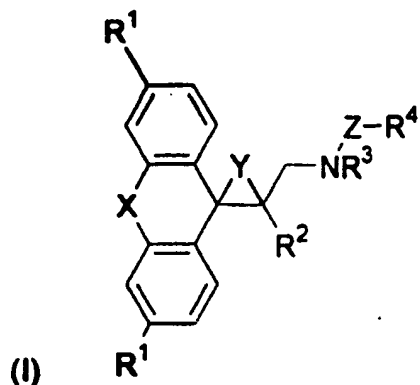
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and

(4) reacting said compound of formula (VI) with compound selected from the group consisting of: (a) sodium acetate and R^4COCl ; (b) CDI and R^4CO_2H ; (c) $EtN=C=N(CH_2)_3NMe_2 \cdot HCl$; (d) R^4CO_2H ; (e) $ClCO_2R^4$; (f) $ClC=O(NHR^4)$; and (g) R^4SO_2Cl to obtain a compound of formula (I).

15

68. A method of making a compound having the formula:



wherein **X** is a single bond, hydrogen, sulfur or NR^5 , $(\text{CH}_2)_n$ wherein n is an integer from 1 to 3; $-\text{HC}=\text{CH}-$; and $-\text{CH}_n\text{W}$ wherein **W** may be oxygen, sulfur or NR^6 ;

R¹ is from one to three substituent groups each selected from the group consisting of lower alkyl ($\text{C}_2 - \text{C}_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

R² is a phenyl group in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($\text{C}_2 - \text{C}_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile, a heteroaromatic ring selected from the group consisting of substituted- or unsubstituted thiophene, furan, pyrrole, or pyridine;

wherein **Y** is $-\text{CH}_2-$ or hydrogen;

R³ is hydrogen;

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Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone;

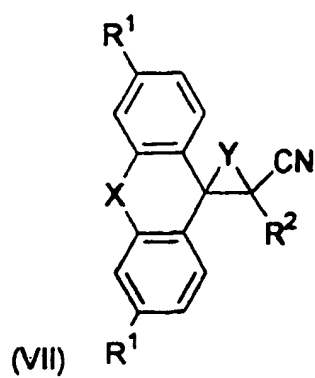
R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenylloweralkyl in which said phenyl group is substituted with hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted- or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted-or unsubstituted thiophene, furan, pyrrole or pyridine; and

R⁵ is selected from the group consisting of: hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl, in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl (C₂ - C₆), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido, or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile comprising the steps of

(1) reacting DiBAL with a compound having the formula (VII):

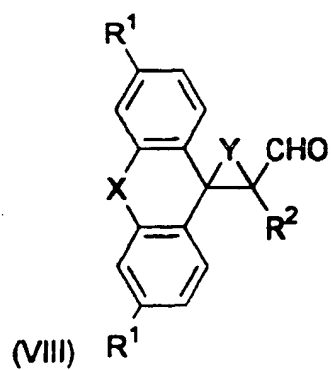
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to obtain a compound having the formula (VIII)

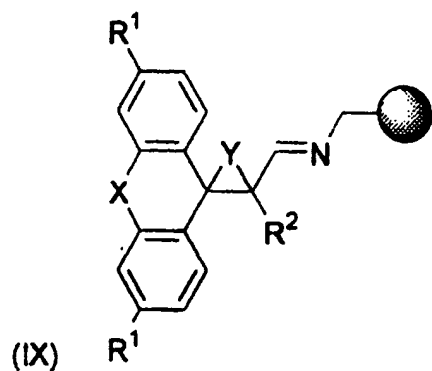
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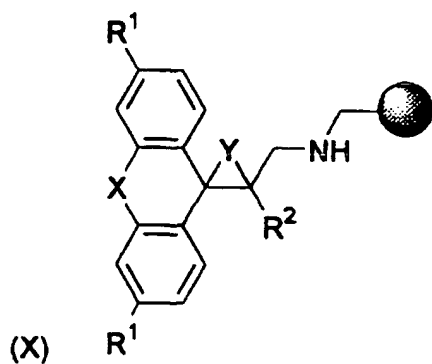
(2) reacting said compound of formula (VIII) with Rink resin to give a resin-bound compound of formula (IX):

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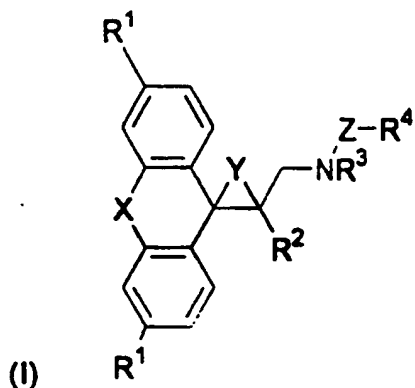


(3) reacting said compound of formula (IX) with sodium triacetoxyborohydride to form a compound of formula (X):



(4) reacting said compound of formula (X) with R^4CO_2H in the presence of HATU and DIEA followed by treatment with TFA to form a compound of formula (I):

69. A method of making a compound having the formula:



wherein **X** is a single bond, hydrogen, sulfur or NR^5 , $(\text{CH}_2)_n$ wherein *n* is an integer from 1 to 3; $-\text{HC}=\text{CH}-$; and $-\text{CH}_2\text{W}$ wherein **W** may be oxygen, sulfur or NR^6 ;

R¹ is from one to three substituent groups each selected from the group consisting of lower alkyl ($\text{C}_2 - \text{C}_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile;

R² is a phenyl group in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($\text{C}_2 - \text{C}_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile, a heteroaromatic ring selected from the group consisting of substituted- or unsubstituted thiophene, furan, pyrrole, or pyridine;

wherein **Y** is $-\text{CH}_2-$ or hydrogen;

R³ is hydrogen;

Z is selected from the group consisting of carbonyl; carboxy; carbonylamino; or sulfone;

R⁴ is straight- or branched-chain alkyl having from 2 to 12 carbon atoms; phenylloweralkyl in which said phenyl group is substituted with

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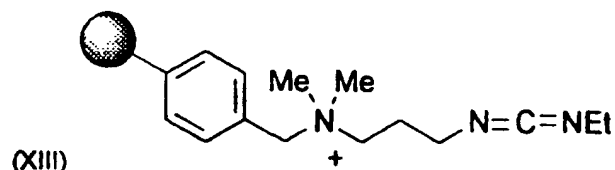
hydrogen or with one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile; a heteroaromatic ring such as substituted- or unsubstituted thiophene, furan, pyrrole, pyridine, or a heteroaromatic ring connected by a lower alkyl chain wherein said heteroaromatic ring is chosen from substituted- or unsubstituted thiophene, furan, pyrrole or pyridine; and

R^6 is selected from the group consisting of: hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; phenyl, in which said phenyl group is substituted with hydrogen or from one to three substituent groups each selected from the group consisting of lower alkyl ($C_2 - C_6$), lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido, or nitrile; phenyl lower alkyl in which said phenyl group is substituted with hydrogen or with from one to three substituent groups each selected from the group consisting of lower alkyl, lower alkoxy, hydroxy, halo, carboxy, carboalkoxy, amino, amido, sulfonamido or nitrile comprising the steps of

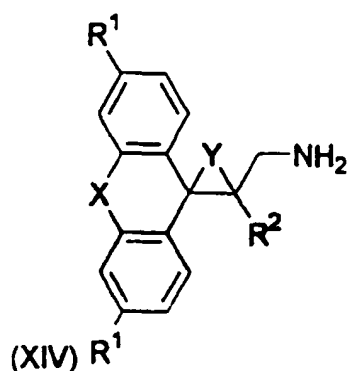
(1) reacting said compound of formula (XII) with Merrifield resin to form a compound of formula (XIII):



to obtain a compound of formula XIII



(2) reacting said compound of formula XIII with a compound of formula XIV and an appropriate acid R^4CO_2H



to obtain a compound of formula (I)

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70. A method of treating inflammatory conditions comprising applying to the skin of a mammal a compound formula (I).

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71. A compound according to claim 1, having the name N-(2-thiophene)acetyl-2, 3, 3-triphenylpropylamine.

72. A compound according to claim 1, having the name N-(5-methylthiophene)acetyl-2-phenyl-3, 3-bis (4-fluorophenyl)propylamine.

73. A compound according to claim 1, having the name N-(3-indolyl) acetyl-2, 3, 3-triphenylpropylamine.

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74. A compound according to claim 1, having the name N-(2-carbonyl-5-methylthiophene) -2-(9H-fluoreny-9-yl)-2-phenylethylamine.

75. A compound according to claim 1, having the name N-(2-chlorophenyl)acetyl-1, 2, 2-triphenylcyclopropylmethylamine.

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76. A compound according to claim 1, having the name N-(2-thienyl)carbonyl-1, 2, 2-triphenylcyclopropylmethylamine.

77. A compound according to claim 1, having the name N-(phenyloxy)carbonyl-1, 2, 2-triphenylcyclopropylmethylamine.

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78. A compound according to claim 1, having the name N-(4-chlorophenoxy)carbonyl-1, 2, 2-triphenylcyclopropylmethylamine.
- 79 A compound according to claim 1, having the name N-(2-pyridine)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.
- 80 A compound according to claim 1, having the name N-(4-n-butoxyphenyl)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.
- 81 A compound according to claim 1, having the name N-(2, 4-difluorophenyl)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.
- 82 A compound according to claim 1, having the name N-(2-thiophene)carbonyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.
- 83 A compound according to claim 1, having the name N-(3-cyanophenyl)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.
- 84 A compound according to claim 1, having the name N-(2, 4-difluorophenyl)carbonyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.
- 85 A compound according to claim 1, having the name N-(4-fluorophenyl)acetyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.
- 86 A compound according to claim 1, having the name N-(4, 5-dichlorophenyl)carbonyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.

- 87 A compound according to claim 1, having the name N-(3-methylphenyl)acetyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.
- 5 88 A compound according to claim 1, having the name N-(phenyl)acetyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.
- 89 A compound according to claim 1, having the name N-(5-chloro-2-benzothiophene)acetyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.
- 10 90 A compound according to claim 1, having the name N-(2, 4-difluorophenyl)carbonyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.
- 91 A compound according to claim 1, having the name N-(4-trifluoromethylphenyl)acetyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.
- 15 92 A compound according to claim 1, having the name N-(phenyl)acetyl-2- (4-trifluoromethylphenyl)-3, 3-diphenylpropylamine.
- 93 A compound according to claim 1, having the name N-(4-fluorophenyl)acetyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 20 94 A compound according to claim 1, having the name N-(3, 5-bis-trifluorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 95 A compound according to claim 1, having the name N-(4-chlorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 25 96 A compound according to claim 1, having the name N-(3, 4-dichlorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.

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- 97 A compound according to claim 1, having the name N-(2-fluorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 5 98 A compound according to claim 1, having the name N-(2-fluorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 99 A compound according to claim 1, having the name N-(4-fluorophenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 10 100 A compound according to claim 1, having the name N-(4-trifluoromethylphenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 101 A compound according to claim 1, having the name N-(3, 5-bistrifluoromethylphenyl)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 15 102 A compound according to claim 1, having the name N-(2-thiophene) carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 103 A compound according to claim 1, having the name N-(5-methyl-2-thiophene)carbonyl-2- (4-iodomethylphenyl)-3, 3-diphenylpropylamine.
- 20 104 A compound according to claim 1, having the name N-(4-chlorophenyl)carbonyl-2- (3, 4-methylenedioxyphenyl)-3, 3-diphenylpropylamine.
- 25 105 A compound according to claim 1, having the name N-(2-propyl) carbonyl -1, 2, 2-triphenylcyclopropylmethylamine.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/27712

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C233/12 C07C233/16 C07C233/30 C07C233/40 C07C233/51
C07D213/56 C07D333/36 C07D333/24 A61K31/165 A61K31/38
A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 11880 A (MERCK SHARP & DOHME ;CHAMBERS MARK STUART (GB); HARRISON TIMOTHY () 4 May 1995 see page 1; examples 11-20 ---	1,49
A	FR 2 354 997 A (HEXACHIMIE) 13 January 1978 see claims 1-6 & BE 855 689 A cited in the application ---	1,49
A	US 4 822 780 A (TSUDA YOSHIHIKO ET AL) 18 April 1989 see abstract --- -/--	1,49



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

6 April 1999

Date of mailing of the international search report

20/04/1999

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Authorized officer

Rufet, J

INTERNATIONAL SEARCH REPORT

Interv. .nal Application No

PCT/US 98/27712

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>GI HYEON BAEK ET AL.: "Homovanillic amide derivatives as capsaicin analogs and their analgesic activity"</p> <p>ARCH. PHARM. RES., vol. 20, no. 5, October 1997, pages 659-661, XP002098829 see page 660</p>	1,49
A	<p>BENJAMIN BLANK ET AL.: "Synthesis and antialdosterone activity of substituted 2,3,3-triphenylpropylamines"</p> <p>JOURNAL OF MEDICINAL CHEMISTRY., vol. 12, 1969, pages 873-876, XP002098830 WASHINGTON US cited in the application see page 874, column 2, paragraph 6</p>	1,49

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/27712

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 70
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Although claim 70 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 70

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/27712

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9511880	A	04-05-1995	AU 7947594 A	22-05-1995
FR 2354997	A	13-01-1978	BE 855689 A	15-12-1977
			CH 603553 A	31-08-1978
			DD 129902 A	15-02-1978
			DE 2726993 A	29-12-1977
			DK 265277 A	17-12-1977
			GR 58465 A	12-10-1977
			JP 53007654 A	24-01-1978
			NL 7706364 A	20-12-1977
			PT 66589 A,B	01-06-1977
			SE 7706895 A	17-12-1977
			ZA 7703350 A	26-04-1978
US 4822780	A	18-04-1989	NONE	

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